A VARIANT OF RHEUMATOID ARTHRITIS CHARACTERIZED BY RECURRENT DIGITAL PAD NODULES AND PALMAR FASCIITIS, CLOSELY RESEMBLING PALINDROMIC RHEUMATISM

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Introduction

Observations culminating in the work of Nichols and Richardson in 1909 clearly differentiated rheumatoid arthritis from degenerative joint disease, a distinction which has been universally accepted and has done more to clarify our ideas on chronic rheumatism than any other single concept. Rheumatoid arthritis itself, however, has tended since then to become an unwieldy nosological hotch-potch, including almost any chronic joint affliction which is not obviously exogenous (for example traumatic or bacterial) in origin. Many have suggested that the term includes a variety of diseases, and attempts have been made to separate out such clinical entities as:

(a) infective arthritis, characterized by the involvement of a few large joints and the presence of a focus of infection, but no recoverable metastatic organism and by a tendency to improve or even to heal following the removal of the focus;

(b) classical rheumatoid arthritis, occurring in middle-aged women and involving, characteristically, multiple finger joints;

(c) psoriatic arthritis, characterized by terminal interphalangeal joint involvement and association of activity with skin exacerbations;

(d) joint disorders associated with ulcerative colitis and other intestinal diseases (for example Whipple's syndrome), characterized by a relatively mild course with remissions and exacerbations dependent on activity of the primary disease;

(e) spondylitis ankylopoietica or, as some prefer to call it, rheumatoid arthritis of the spine, differing in the earlier age and preponderantly male incidence: its peripheral joint manifestations are different neither clinically nor pathologically from those of rheumatoid arthritis "proper";

(f) intermittent hydrarthrosis and palindromic rheumatism (Hench) which are thought by some, but not by Hench, to be variants of the rheumatoid arthritis syndrome; certainly some cases of intermittent hydrarthrosis ultimately develop the same type of permanent joint involvement as in rheumatoid arthritis: see later discussion;

(g) Still's disease. This is rheumatoid arthritis occurring in children and the so-called distinguishing features (for example late radiological involvement) are due only to the increased cartilage protection of epiphyseal bone at this age. Other features, such as pericarditis, enlarged glands, and spleen, are seen in adults as well;

(h) arthritis associated with visceral disseminated lupus erythematosus (see later discussion);

(i) Felty's syndrome with arthritis, splenomegaly, anaemia, leukopenia, and pigmentation of the skin is now generally agreed (for example Talkov and others, 1942), to be rheumatoid arthritis, occasionally complicated by coincident disease such as cirrhosis of the liver: in the classical rheumatoid case, any or rarely all of these extra signs may be present;

(j) Sjögren's syndrome (rheumatoid arthritis with kerato-conjunctivitis sicca).

Thus, we have a number of loosely conceived nosological entities of whose life course we know as yet little and whose pathological changes, still ill-understood, appear superficially to resemble each other very closely. These various syndromes are statistically determined rather than true entities, based on clinical or anatomical data rather than a knowledge of aetiology. The chief reason for distinguishing between them is the practical usefulness of such distinctions for prognosis and treatment. For scientific purposes, the resemblances between these various conditions are, from many angles, more important than their differences; it seems probable that the basic (and unknown) pathological processes are, in all, similar in nature. This means that these conditions may be considered as variants on a basic theme, or from a basic type. Such variants fall into several possible categories. The variation-producing factor may be constitutional (for example, the congenital ductus arteriosus variant of subacute bacterial endocarditis); it may be age of onset (for example, Still's disease); it may be modification by environmental factors, such as nutritional state, etc., or it may be the presence of some other disease producing a pseudovariant (for example, cirrhosis of liver complicating rheumatoid and producing Felty's syndrome). There might be variation in original exogenous stimulus (for example, antigen)—or variation in the type or location of tissue originally stimulated. Of such vagaries we know very little—why some patients with rheumatoid develop eye lesions and others do not, why some psoriatics develop arthritis and others do not—but to "account" for the variant we postulate some extra factor, operative before or after the onset of the main disease, either determined by it or actually determining the main disease.

A further characteristic of such variants is that a gradation exists between the type and its variant. Thus we do not include rheumatic fever as a variant of rheumatoid arthritis because we do not see cases which are pathologically halfway between rheumatic fever and rheumatoid arthritis; our patients turn out ultimately to have either permanent joint or permanent heart disease or neither (in contra-distinction to those of other clinics, for example, Baggenstoss and Rosenberg, 1941; Bayles, 1943; Young and Schwedel, 1944). Thus, to prove a syndrome to be a variant, it is necessary to establish the existence of lesser and variable degrees of variation from type, that is, transitional forms.

It is the object of this paper to detail such a variant. A case will first be described (in full detail since it appears to be unique) which shows the variation at a maximum, so much so that the correct diagnosis was not reached for nine years: following this, other cases will be detailed rather more shortly, showing transition to the more usual type of rheumatoid arthritis.

Case Histories

Case 1

E.P., a man aged 60, on his first admission (Feb. 2, 1943) with no family history or relevant disease, had been in good health until the age of 51, except for a minor degree of silicosis contracted during service as a mining engineer in South Africa, for which he was invalided at the age of 45. He had contracted no tropical disease. The present complaint started in 1934 at the age of 51* following an exposure to damp and cold: the hands became swollen and painful in attacks lasting some two or three days. At this period he had perhaps two attacks every month, affecting only the hands and feet. These are described as swellings and pain in the neighbourhood of the proximal interphalangeal joints, one or two being affected at each incident, and then perhaps others in succeeding incidents. These attacks continued to 1935, being always more frequent during the winter months, but completely absent in a warm climate (South Africa in December 1935 and January 1936) and returning on the voyage home.

In October 1935 the patient saw Consultant I (Medicine) complaining at that time of "superficial painful swellings on the toes, fingers, wrists, knees, and soles of feet, especially marked in cold weather".

* The patient's wife was medically qualified and kept a detailed diary of her husband's condition and copies of the medical reports from the numerous specialists whom he consulted; I am much indebted to her for allowing me to see and use these documents, as well as to the consultants themselves.

Examination showed nothing abnormal except a small oedematous area appearing during examination between the index and middle knuckles of the left hand, which disappeared in a few minutes. In between these attacks the patient was perfectly well. For example:

"*Aug. 2.*—Swelling of right little finger.
Aug. 6.—Finger better.
Aug. 7-8.—Right wrist painful.
Aug. 9.—Wrist free of pain. Got slightly chilled: by evening the right index finger was considerably swollen with clear distal demarcation, swelling covering one inch above and below middle phalangeal joint; middle finger also swollen. Left hand: middle finger swollen and similar to right index. Feet: uncomfortable but not definitely swollen.
Aug. 10.—Swelling of fingers improved.
Aug. 11.—Fingers improved but swelling started over fifth metacarpals on both hands.
Aug. 13.—Hands much improved.
Aug. 15.—Very slight swelling over first metacarpophalangeal joint.
Aug. 17.—Slight trace of swelling remaining.
Aug. 22.—Slight discomfort, but no real swelling.
Sept. 1.—Slight swelling of third left finger.
Sept. 4.—Painful swelling over first metacarpal left hand. Feet painful. Right hand also uncomfortable.
Sept. 5.—Right hand swollen and middle finger very tense. Left hand still swollen: middle finger tense. Feet painful.
Sept. 6.—Most of swelling of right hand improved, but hard swelling appearing under middle and third finger tips. Left hand better. Feet still painful.
Sept. 7.—Left hand worse again, swelling over first knuckles, middle finger tense. Right hand and fingertips improved; feet extremely painful with hard swellings under heads of metatarsals.
Sept. 9.—Both hands much swollen and feet painful. Contraction of fourth finger of right hand owing to swelling over tendon. Hard swelling over olecranon. Spent day in bed.
Sept. 11.—Saw Consultant II (Physical Medicine). Hands subsided. Fourth finger of right hand contracted.
Sept. 13.—Sufficiently well to play three sets of tennis.
Sept. 15.—Saw Consultant III (Allergy) who after testing for protein reactions pronounced condition to be non-allergic. Swelling almost vanished from hands with exception of fourth finger left hand. Right fourth finger still contracted. Fluid in left olecranon bursa.
Sept. 16.—Fourth left finger tense. Wrists both painful.
Sept. 18-22.—Much improved.
Sept. 27.—Still some contracture of tendon of fourth finger right hand and fluid in left olecranon bursa. Generally comfortable in the morning, but in the afternoon the right foot was painful with very tender spot below right outer malleolus.
Sept. 29.—Both hands and all fingers tense and swollen. Feet painful." (Extracted from diary.)

In October 1936 he was seen by Consultant IV (Medicine). He was complaining at that time of puffy swellings on the back of the hand with tenseness of fingers and wrists, swelling of the soles of the feet, and small shotty nodules in the olecranal bursa which showed effusion and hard nodular swelling on both ulnae. There was a premonitory sensation of tenseness and then swelling arising in two to three hours, sometimes taking days to subside. This was brought on by cold weather but left no permanent change. A tentative diagnosis of gout was made and the patient was treated with aspirin and colchicum. No improvement having followed a holiday in Bermuda in April 1937, he was sent into a private clinic under the care of Consultant V (Gastro-enterology), where the condition was thought to be gout. Blood uric acid was 3·6 and later 3·2 mg. per 100 c.cm. Atophan at first seemed to be helpful, causing the swellings to disappear for a few days, but subsequently it had much less obvious effect. The erythrocyte sedimentation rate was recorded as 62 mm. and 4 mm. per hour (Westergren) one month later. Haemoglobin was 96 per cent., red cell count 4,900,000 and white cell count 10,000 per c.mm. of blood, 70 per cent. polymorphs, and later 7,600, 62 per cent. polymorphs. Consultant VI (Ear, Nose, and Throat) found no nasal or pharyngeal infection. Urine was sterile and normal. Cholecystogram showed no gall-bladder shadow and it was thought that gall-stones were present, but as there was no evidence of cholecystitis it was decided to leave them. Previous to this investigation he had been having about twenty attacks yearly in the preceding three years. These were lasting something like a week.

After the patient left the clinic the diary records much the same pattern as before, of daily stiffnesses and swellings attacking hands, feet, wrists, and shoulders, with painful swellings over the olecranal processes of both ulnae, alternating with periods of freedom permitting a normal life, including golf.

In the following two years, 1938 and 1939, he had very few attacks indeed, none or one or two a year. In 1940, however, he had a few more attacks, something like six per year, each lasting two or three days. At this time he was working very hard. In the summer of 1941 the attacks became more frequent, about twenty per year, and, although atophan was increased in dosage, no benefit was obtained. In October 1941 he saw Consultant VII (Rheumatism) who thought the condition was an angioneurotic oedema possibly due to infection. White blood cells were 10,000 per c.mm. with 3 per cent. eosinophils, 2 per cent. monocytes, 73 per cent. polymorphs, and blood uric acid 2·5 mg. per 100 c.cm. During the active phase the erythrocyte sedimentation rate was 30 mm. in one hour (Westergren) and blood uric acid 3·4 mg. per 100 c.cm. A large gall stone was demonstrated by radiography and removal was recommended.

During November 1941 the diary records daily involvement of one or two joints, fingers, wrist, or forearm, with swelling and pain, often unilateral or alternating, lasting two or three days and then remitting, only to involve fresh joints: para-articular puffy tender swellings over the back of the hand, the size of a brazil nut, were noted together with further shotty nodules along the shaft of the ulna and in the pads of the digits. There was also noted on one occasion tenderness and contraction of the palmar fascia producing a transient contracture of the right middle and ring fingers, as had been seen previously.

Consultant VIII (Medicine) was seen in January 1942.

"Has an attack now, began two days ago. Now has a diffuse though patchy oedema scattered over hands, wrists, forearms. Areas are red, taut, not tender. Joints free. Also periosteal nodes, of which there are now two on ulna. They come quickly but go very slowly. . . . Both legs are now swollen with oedema that will come and go in twenty-four hours. No evidence of food allergy."

Because of radiological involvement the right antrum was operated on and showed some muco-pus growing staphylococcus albus. No finger swellings were seen until three weeks later, the day before discharge. As a *Strep. faecalis* vaccine showed delayed positive skin reaction a course of injections was given but with no result. Transitory two-day swellings continued, affecting both hands, varying fingers, left forearm, both elbows. Atophan produced no improvement. Radiological examination of elbows, knees, showed no abnormal bony change. On June 16, right index finger and left middle finger were swollen and the right olecranon bursa became swollen and painful. Fluid from this bursa showed pus cells and *Staphylococcus aureus*. Radiograph of chest showed silicosis. Blood count (July 2) 100 per cent. Hb. White cell count 6,700 per c.mm. of blood, 61 per cent. polymorphs, 2 per cent. eosinophils, monocytes 6 per cent., lymphocytes 31 per cent. Erythrocyte sedimentation rate (Wintrobe) 16 mm. in one hour. Blood uric acid 3·6 mg. per 100 c.cm."

Consultant IX (Thyroid Surgeon) thought that the oedema of the ankles was due to right-sided cardiac insufficiency associated with silicosis and emphysema. On Sept. 14, 1942, he was seen in conjunction with Consultant X (Rare Diseases) who thought it "belonged to the angioneurotic oedema, Raynaud group. The swelling of the hand which had come up quite quickly today showed a large central swelling, blanched, and surrounded by another area almost cyanotically red. The bony prominences disappear like the soft swellings but take longer: the most recent one is over the head of the fibula. These attacks are associated with cold weather. Final opinion, angioneurotic oedema with intermittent hydrarthrosis." (The case has since been briefly recorded by Dr. Parkes Weber (1946) in a discussion of palindromic rheumatism.) Therapeutic suggestions were autohaemotherapy, shock therapy, penicillin, adrenaline, atophan, "opondon" and "testoviron" and pituitary extract. The latter five preparations were tried without improvement.

Recent History obtained from the Patient.—During 1942 he had about fifty attacks, each lasting on the average two or three days, and was never really clear from the condition. Only in the past year had the wrists been affected. The ankles had shown pitting only for the six months before entry to hospital, at which time there were four varieties of lesion complained of: (1) tautness and swelling of the proximal phalangeal joints of the hands and feet with spindling, (2) small intracutaneous lumps mainly in the pads of the fingers and thumbs; these were tender and painful, came up in two days, and lasted for one month or longer, (3) nodules over the olecranon lasting two or three months and sometimes longer; nodules over the hip had been there since October 1942. These larger nodules over bony prominences had been permanently present only for the past year. He had also had (4) some diffuse swelling over the wrist joint and carpus. It was only during the year before entry that the fingers had remained swollen between attacks.

Examination on Feb. 12, 1943.—The pupils were examined and the fundi found to be normal; there was no iritis. Throat and ears were normal. The venous pressure in the neck was not increased. There was emphysema. The heart sounds were faint and regular, with no added sounds. All reflexes were present and normal. Blood pressure was 130/85 mm. Hg. There was a soft mass on the right hypochondriac region of the abdomen (? gall-bladder). The testicles were normal. The glands in the right axilla were enlarged but not tender; in the left axilla, both groins, and right epitrochlear region, they were palpable but not enlarged.

Nodules were seen (1) subcutaneously over the crests of the left and right ulnae (Fig. 1a), over the bony portion of the right hip (greater trochanter), fixed to periosteum, and over the fibula head on the left side. (2) Small nodules were palpable in the top of the finger pads (Fig. 1b). Two of these were present on each of the thumbs, and one had just subsided at the base of one of the fingers on the palmar aspect. They were not very tender.

Joints.—There was free movement of all joints (except an old injury affecting the metacarpo-carpal joint of the right thumb). There was some swelling with tautness and shiny atrophy of the skin (a slight cyanotic appearance also) over the proximal interphalangeal joints of the left second, third, and fifth, and the right hand fifth fingers (Fig. 1b). Two days after the first examination there was some slight swelling noticed over the carpus and wrist on the back of the left hand. The ankles showed pitting oedema. There was some swelling of the phalangeal joints of several toes. The knees, elbows, shoulders, and hips were normal.

Investigations.—The temperature was normal throughout the patient's stay in hospital. The pulse was about 70 per minute.

Urine.—The specific gravity was 10,12-10,16. The urine was acid, with no albumin, sugar, or blood.

Blood Chemistry.—Uric acid was 2·9 mg. per 100 c.cm. of blood during an attack and 2·8 mg. later. Cholesterol was 198 and 174 mg. per 100 c.cm., serum calcium 12 and 10·9 mg., phosphate 3·9 mg., alkaline phosphatase 11 K.A. units, plasma proteins 5·1 g. per 100 c.cm. (albumin, 2·7 g., globulin 2·2 g., fibrin 0·2 g., and the albumin globulin ratio 1·2).

Sedimentation Rate.—This was 9 mm. in one hour (Westergren) in duplicate, and later 15 mm. in one

hour in duplicate. Plasma protein was later 6·7 g. per 100 c.cm.

Heart.—The electrocardiogram showed a right axis shift, P.R. interval 0·24 seconds, ST_2 and $_3$ elevated.

Blood Count.—Haemoglobin was 13·4 g. per cent., the red cells 4·6 million, and the white cells 5,000 per c.mm. of blood (51 per cent. polymorphs, 47 per cent. lymphocytes, 2 per cent. monocytes, no eosinophils).

Radiological Investigation showed, in the feet, some lipping and a small " cystic " area of rarefaction on the medial side of the right first metatarsal head (Fig. 2). The fifth right metatarsal head showed decalcification, loss of the subchondral boundary line, and considerable irregularity of the articular surface. The most remarkable feature of the hands (Fig. 3) was decalcification of the juxta-articular cortex of the left third and fifth proximal phalangeal heads on their radial sides; where the articular surface abuts on this area, slight erosion was seen, with small subchondral areas of rarefaction. Similar subchondral translucent areas were seen in the head of the second left proximal phalanx. In the right hand the fifth proximal phalangeal head showed similar rarefaction and loss of the normal subchondral boundary line; three months later it showed further marked loss of definition and small cystic areas. It will be noticed that these joints are those which were permanently swollen clinically (Fig. 1b). These changes were observed before biopsy was undertaken: they were not visible in radiographs made one year before (April 1942) and therefore coincide with the onset of permanent swelling.

Biopsy was performed on the subcutaneous nodules on the olecranon processes of both sides, on the bone lesion and joint of the third left proximal phalanx, and on one of the small left thumb-pad nodules. The appearance of the olecranon nodules was grossly that of a rheumatoid nodule. When the thumb-pad nodule was incised, a small amount of pus escaped. When incision was made over the bone cyst just proximal to the proximal interphalangeal joint, a small cyst was seen lying on top of the periosteum with its neck towards the joint cavity. This was removed; it was difficult to be certain whether it communicated with the joint. On the periosteum being incised with a gouge, a small gush of pus was noticed from which culture and smears were taken (as also from the thumb-pad node). Smears from both lesions showed mainly monocytes with a blue cytoplasm containing many small vacuoles and sometimes ingested polymorphs. There were also 20 per cent. polymorphs, some of them degenerate, some containing similar small vacuoles. The cultures from both lesions were sterile (blood agar and 5 per cent. serum broth, anaerobic and carbon dioxide-enriched aerobic culture).

Microscopic Examination showed the nodule from the right elbow to consist of old whorled fibrous tissue in which were embedded many small vessels, some of them surrounded by a few lymphocytes and monocytes (non-specific change). The nodule from the left elbow (Fig. 4) consisted of a series of necrotic cavities, some filled with blue-staining debris, some with dense swollen collagen fibres, some with recent fibrin strands. These centres were surrounded by a thick palisade layer of fibroblasts, containing many lymphocytes, monocytes, plasma cells, and polymorphs. The structure was a typical nodule of rheumatoid arthritis. In the tissue from the terminal digital pad of the thumb immediately beneath the epidermis was a structure closely resembling a rheumatoid " necrobiotic " nodule (Fig. 5), but rather more " biotic " than " necrotic ". The central area of acute necrosis contained less collagen, but many degenerate cells, many of a monocyte nature, and some fibrin. Some eosinophils were seen in one portion. The superficial portion contained peculiar histiocyte nests, composed of the same cells as took parts in the palisade, but without central necrosis, judged by serial sections and at an earlier stage judged by the finer reticulum network.

The cyst from the third proximal finger showed synovial membrane with marked proliferation and inflammatory changes; at one place strongly eosinophil granules were seen in a small cell nest surrounded by giant cells (Fig. 6); these did not appear to be derived from eosinophil leucocytes, and were possibly derived from collagen degeneration: strips of cartilage were embedded in the granulation tissue.

The bone lesion showed some osteoclastic resorption of spicules and foamy fibrous tissue with a cyst (Fig. 7) containing monocytes similar to those found in the pus smear (Fig. 8).

The following possibilities were considered: palindromic rheumatism (Hench), rheumatoid arthritis, intermittent hydrarthrosis, sarcoidosis, gout, angio-neural arthrosis (Solis-Cohen), and allergic rheumatism (Kahlmeter). The occurrence of bony change, the residual spindling, and the results of biopsy favoured the diagnosis of rheumatoid arthritis, although the very acute character of the lesions and the long recurring course without any serious articular damage argued an atypical case. The early history closely resembled that of palindromic rheumatism, but the low cholesterol was against this diagnosis. The other five possibilities discussed had little to recommend them. There was no heart failure judged by jugular pressure rise, but the presence of silicosis and emphysema warranted caution.

The essential lesion was a recurrent focal necrosis with inflammatory reaction of a rheumatoid nature affecting the tissues in the neighbourhood of joints, bursae, tendon sheaths, and finger pads.

Diagnosis.—A diagnosis was made of rheumatoid arthritis, silicosis, emphysema, and cholelithiasis.

Treatment.—The treatment prescribed was: a full, high-vitamin diet, assisted active exercises following light massage, and no drugs except sodium salicylate, bicarbonate, and ascorbic acid. Deep *x*-ray therapy was also suggested.

After the patient's discharge from hospital (Feb. 18, 1943), painful swellings developed over the heads of the second and third right metatarsals and fifth left metatarsal bones after walking for the first time. Consultant XI (Radiology) reviewing the *x*-ray plates, was " not convinced that there was anything to justify the diagnosis of rheumatoid or even infective arthritis other than

possibly the joint swelling", and he "considered that the apparent loss of cartilage was an artefact". (Flakes of cartilage undergoing dissolution were seen lying in the synovial membrane from the excised cysts, as frequently seen in synovial membrane of rheumatoid arthritis. These cysts were undoubtedly herniations from a joint which had been used while still containing increased fluid.) Consultants XII and XIII (Pathology) saw the sections of synovial membrane and suggested that the condition might be sporotrichosis, as the patient had been in a South African mine in 1927 where an outbreak occurred. As iodine offers a cure for sporotrichosis, this suggestion was received enthusiastically, despite the completely atypical clinical story, and in our own opinion the likeness of the nodules to those of rheumatoid arthritis. He was admitted for the second time (April 7, 1943), and a further biopsy of the fifth proximal interphalangeal joint (Fig. 9) merely confirmed the previous findings: another pathological consultant (XIV) said the nodules were identical with those from cases of rheumatoid arthritis. Fresh tissue and swabs of the pus from the synovial membrane and from the finger were examined and were cultured on Sabouraud and numerous other media as well as being injected into rats by ourselves and by Dr. Duncan (Mycology). All these investigations were sterile.

While the patient was in hospital his condition was much as before. He was afebrile, and the sedimentation rate was 12 mm. in one hour (Westergren). He had a troublesome attack of bronchitis which had subsided before the second admission. The electrocardiogram showed, as before, prolonged P.R. interval (0·26 sec.), elevated ST interval in leads II and III, and a right axis shift. A radiograph of the chest showed the left ventricle to be slightly enlarged, the transverse diameter being 5½ inches. There was some slight prominence of the pulmonary artery. Emphysema and small silicotic nodules were seen throughout the lung with some *increased hilar* shadowing. Further investigations were as follows: Brucella agglutinations negative. G.C. fixation test negative. Wassermann and Kahn tests negative. Blood urea 54 mg. per 100 c.cm. of blood; cholesterol 187 and 197 mg.; plasma phosphates 3·6 mg.; plasma protein 7·0 g.; plasma phosphatase 12 K.A. units per 100 c.cm. Hb. 11·0 g. per cent. He was discharged from hospital three days after entry (April 7, 1943) for a therapeutic test with iodine. For one week on placebo he was normal, but he developed pyrexia and general discomfort twelve hours after starting iodine.

His condition improved after stopping the iodine, but later (June 20) there was "no real improvement in the details of his condition. *Hands*: The nodules in his fingers have been very troublesome up to the last few days, but for the moment have somewhat subsided. The joints are still swollen, both the two that were biopsied (proximal interphalangeal joint of left third and right fifth fingers) and the proximal interphalangeal of the fourth right and the terminal joint of the first left finger. Wrists have been swollen, now better. There have been two slight bouts of oedema of dorsum of both hands, that on the left hand still persisting slightly. *Forearms*: Painful nodule middle of shaft left ulna. *Elbows*: left has been swollen and painful, now better. Right has a very painful swelling over ulna. *Shoulders*: Right shoulder has been and still is very painful with a swelling approximately over the acromium process. Also painful over region of insertion of deltoid. Such movements as getting hand into pocket and raising the arm are difficult and painful, and so is lying on that side. Left shoulder not painful except when he has been lying on it. *Feet*: dorsum right foot swollen and movement of big toe joint painful. Walking not good. Oedema of ankles much improved. Still very limited in choice of shoes. *Knees*: very painful, 'set' after they have been kept in one position and are difficult to get moving again—improve upon movement. Swellings over medial and lateral condyles of femur and over left patella. He is still taking salicylates and vitamin C, and still having massage which, I think, has definitely helped his feet but does not seem to ease his shoulder or his hands much."

Consultant XV (Medicine) suggested lipoidosis. Arrangements were made for the patient to go for a course of spa treatment in addition to diet, massage, exercises, salicylates, and phenobarbitone.

After the patient had had a course of spa treatment, Consultant XVI (Rheumatism) was of the impression that the condition was "a fibrositis of the periarticular type".

The treatment seemed to do him little good. In October 1943, after radiography of sinuses and examination of post-nasal swab, Consultant XVII decided that infected ethmoidal antra were the fount of infection, as a pure and plentiful growth of *Staphylococcus albus* had been reported. Short-wave therapy was begun in November 1943, and continued with occasional intermissions till the autumn of 1944, but produced no improvement. Then protein shock therapy with *E. coli* was tried, but produced no improvement. Small doses of his own serum given subcutaneously did no good. Since February 1945 he had no particular treatment except "Atophan", when his feet seemed particularly "gouty".

One week before the third admission to the Postgraduate Medical School (July 6, 1945) the patient developed dysphagia, tenderness, and swelling beneath the left sternomastoid with fever up to 103° F., and paronychia (July 2) treated with sulphapyridine. Examination showed no throat infection clinically or bacteriologically. There was tenderness and swelling deep to the left sternomastoid. Haemoglobin was 11·4 g. per cent.: white cells numbered 17,000 per c.mm., 75 per cent. polymorphs, blood urea 42 mg. per 100 c.cm., P.R. interval 0·36 seconds. A radiograph showed thickening of the right antrum and backward deviation of trachea in the region of the thyroid. The urine was normal.

Fever, swelling, and leucocytosis disappeared with penicillin, and the sedimentation rate returned to 6 mm. in one hour (Westergren). The cystic mass deep to the sternomastoid, which became palpable with subsidence of the inflammation, itself subsided and the patient was discharged. Six weeks later (Aug. 14, 1945), the lump was scarcely palpable. There was ankle oedema;

the big toe (MTP) joints and the second right (PIP) toe joints were almost fixed. The right forefinger was swollen and tender, the skin shiny and pallid, and the swelling had only come up in the last day or so. There was a healing nodule over the radial side base of the second right MCP shaft (one week old), and small nodules (with central brown depressed area), in the pads of both thumbs and beneath the metatarsal head of the third left toe. There were large subcutaneous nodules on the right ulna (as before), and crops of smaller ones over the elbow region and right knee. Blood uric acid was 3·9 mg. per 100 c.cm. of blood, cholesterol 211 mg. per 100 c.cm., total protein 7·9 g. per 100 c.cm.

Radiological re-examination showed progression of the lesion in the right first metatarsal head, which now showed irregular erosion and complete loss of joint space. The fifth right metatarsal head had recalcified considerably, but showed residual irregularity. The eft first terminal joint now showed a coarse system of translucent spaces involving both proximal and distal phalanges; there was erosion of bone from the margins of the joint affecting both distal and proximal phalanges with destruction of cartilage and complete loss of joint space (Fig. 2). In the hands, destruction of the fifth right proximal interphalangeal joint had occurred. Considerable restitution had occurred in the fifth left PIP joint, which showed only a small area of subcortical rarefaction. The third left PIP joint, however, had progressed to complete loss of joint space and destruction of cartilage with erosion of the articular surface and the formation of patchy cystic areas of translucency. The medullary cavity of the proximal phalanx also showed complete resorption of the normal coarse cancellous bone. The second left proximal phalangeal head showed no progression.

On Aug. 20, 1945, an acute episode of collapse and pain occurred. He was seen by Consultants XVII (Cardiology) and XV. An electrocardiogram next day showed signs compatible with posterior myocardial infarct. Six days later pain and dyspnoea were less, the temperature was 100·4° F., the pulse 42 per minute, and the blood pressure over 100 mm. Hg. Consultant XVIII (Cardiology) found (Aug. 31, 1945) the blood pressure to be 95/65 mm. Hg., the pulse 64 per minute and regular, and the heart enlarged with soft apical systolic murmur, scattered rales, and impaired percussion note at the right base: the liver was easily palpable, but not tender. A further electrocardiogram confirmed the diagnosis of infarct ($ST_{2,3}$ elevation with $T_{2,3}$ inversion and Q waves. No change in P.R. interval (0·36 seconds)). By Nov. 29, 1945, the patient was oedematous with signs of failure despite mersalyl and digoxin. Rheumatoid nodules on both trochanters and both elbows were continually breaking down. The patient died at home on Dec. 20, 1945. No necropsy was done.

Comment.—It is fortunate that this patient's course was so well documented and that notes were available from so many consultants. (The history, incidentally, illustrates in a way not usually recorded the pilgrimage that chronic illness of an unusual kind in the upper income levels may involve and the variety of diagnoses entertained by distinguished specialists.)

The points that need special emphasis are the transient nature of the joint swellings and of the small intracutaneous nodules of the fingers and toes, and the direct relationship of the latter to pressure, the smaller acute swellings in the region of the tendon sheaths and palmar fascia producing transient finger contraction, and the bursitis. The larger permanent nodules over bony sites differed in no way, histologically or clinically, from those seen in rheumatoid arthritis.

Radiological changes were long delayed and atypical. They were attributed to pressure atrophy of bone and herniation of synovial contents into the bone ends as is so frequent in rheumatoid arthritis, but only rarely confined for so long to the non-articulating joint surface as here. I have seen only one other patient with a similar appearance in the proximal phalanx, thought to have rheumatoid arthritis. In the feet the rarefaction of the first distal phalanx can probably be ascribed to a similar process.

The terminal episode was thought to have been coronary ischaemia leading to infarction and failure. The previously prolonged P.R. interval points in the same direction. Unfortunately, the failure to secure a post-mortem examination makes it impossible to say whether this infarction was due to atherosclerosis and thrombosis, due to arteritis or due to obstruction by granulomatous (nodule) tissue such as has been described rarely in the valve ring region of rheumatoid patients (Bagenstoss and others, 1944). Rheumatoid cases with cardiac nodules (Bennett and others, 1940) usually have very widespread nodule formation.

Case 2

The second case showed the same intracutaneous nodules coming up acutely, due to pressure, and the same transient finger contractions: she was a hospital patient throughout, and radiological changes appearing early facilitated the diagnosis.

M.C., a woman aged 28, was admitted on May 14, 1946, complaining of pain and swelling of joints.

Three years before admission she developed pain and swelling of the proximal interphalangeal joint of the right third finger, spreading to the fingers of both hands, and to the wrists and metatarsal regions. Pain was followed by bluish discoloration of the skin and then by swelling. The condition was migratory but often involved several joints at one time. Two years ago the palms of both hands became bright red and, whenever she did any work involving pressure with the

fingers (such as making pastry or pushing a pram), she developed small painful nodules and blisters at the sites of pressure lasting several weeks.

She married about this time and became pregnant nineteen months before admission; this was accompanied (from the second month until the first week of the puerperium) by complete freedom from pain and swelling of the joints, but the colour of the palms was not affected. At the sixth month her cheeks, normally well coloured, became very red, together with her nose, and these symptoms have persisted since. Despite a history of hypertension during pregnancy, delivery was uneventful, but pain, redness, and swelling returned one week afterwards in the wrists, fingers, knees, feet, ankles, shoulders, and elbows and have become worse since. Periods were normal and bore no relationship to skin colour, joint pain, etc. During the last ten months the elbows have become reddened, painful, and nodular; for the last three weeks she noticed a tender nodule over the sacrum and some pain in the neck. She has marked " jelling " after periods of rest.

The family and previous history were irrelevant; there was no history of sore throat.

Examination showed erythema and telangiectases of the nose and cheeks in a " butterfly " distribution with some slight hyperkeratosis but no horny plugs, and little or no atrophy. The palms were markedly reddened over pressure areas and there were splinter haemorrhages in the nail folds of most fingers. Large nodules were present over both olecranon processes and over the sacrum. The heart was normal; the blood pressure 130/80 mm. Hg. No enlarged spleen and lymph glands were found.

There was slight soft tissue thickening of all proximal interphalangeal joints except that of the right thumb, and swelling of the first, second, and fifth metacarpophalangeal joints of both hands (Fig. 10) of the left wrist joint and of the left knee, which contained a small effusion. The grip was weak.

Radiological Examination.—This showed no abnormality in the chest or sinuses. The hands showed typical rheumatoid changes with general rarefaction and erosions affecting both wrist joints and many metacarpal metatarsal and proximal interphalangeal joints. These progressed until one year later (1947) the following joints were grossly affected: metacarpophalangeal right 1, 2, 3, 4, left 1, 2, 3, 4, 5, proximal interphalangeal right 3, left 3 and 4, metatarso-phalangeal right 1, 2, 3, 5, left 3, and both wrist joints.

Bacteriological Examination.—This showed no abnormal flora in the throat; blood and urine cultures remained sterile. The Wassermann reaction was negative.

Dental Examination.—There was no sepsis or caries and only slight gingivitis; radiographs revealed two retained roots.

Haematological Examination.—The haemoglobin was 14·2 g. per cent. The red cell count was 5·2 million per c.mm. of blood, with anisocytosis, anisochromasia, and polychromasis; the white cell count was 4,000 per c.mm., with 65 per cent. polymorphs. The sedimentation rate (Westergren) was 43 mm. in one hour.

Blood Biochemistry.—Plasma cholesterol was 196 mg. per 100 c.cm. of blood; alkaline phosphatase 11·5 K.A. units; albumin 4·2 g. per 100 c.cm., globulin 3·1 g. (and the same a year later), blood uric acid, 1·4 mg. The urine showed a moderate to small amount of albumin during the first five weeks, disappearing later, but neither pus nor casts.

Course.—The day after admission the patient complained of pain in the left shoulder, worse with deep breathing or sitting forward and radiating up the left neck and down the left sternum. Pressure on the chest increased this pain. A pericardial friction rub was heard at all areas, especially at the base, and electrocardiograms showed typical changes. The rub persisted for two weeks and the electrocardiogram changes gradually returned towards normal in five weeks (Fig. 11). A low-grade fever with peaks up to 101° F. persisted during the first two weeks but subsided thereafter together with the pericarditis. Pleuritic pain was noticed a year later but was not associated with a rub, with electrocardiographic, or with *x*-ray abnormalities. Pain consonant with perisplenitis was complained of on several occasions, lasting about three days.

During the next four weeks, while she was under close daily observation in hospital, a remarkable sequence of inflammatory phenomena was observed unaccompanied by any rise in temperature or albuminuria; these phenomena continued without intermission during the following two years* up to the time of writing. They were apparently unaffected by a febrile episode (in August 1946) of cervical adenitis due to tonsillar infection by an undetermined " haemolytic " streptococcus (penicillin-sensitive but not Group A and producing no soluble haemolysin). Rapid cure with penicillin wrought no change in general status; there was no alteration in leucocyte level, from 3-4,000 with 33 per cent. and 53 per cent. polymorphs respectively, and no increase in the already raised blood sedimentation rate.

The most striking of these phenomena were small deep-seated blisters about 2 to 3 mm. in diameter developing mainly in the terminal pads of the fingers but also occurring elsewhere (Fig. 12). They seemed to be initiated by minor traumata; the patient said that the increased incidence in the thumb and index finger at the beginning of the week was related to handling Sunday's hot roast joint. Further, during a period of relative quiescence, a large crop was produced in the left thumb following two attempts to light a cigarette with a new lighter she had been given: within half an hour the thumb became swollen and later developed nodules and deep-seated blisters. We induced one of them within twenty-four hours by firm pressure with a pencil tip. Each blister seemed the end stage of an intracutaneous nodule: it started as a firm, indurated, and palpable swelling about 5 mm. in diameter, paler than the surrounding digital skin, appearing rapidly and gradually disappearing after a few weeks, passing through a stage resembling a small 2 mm. diameter blister in the centre

* The following account is compiled from notes made when the patient was in hospital and at regular out-patient visits, as well as from a daily diary kept by the patient covering a period of three months.

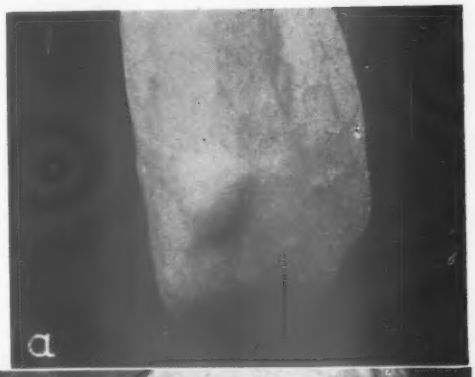
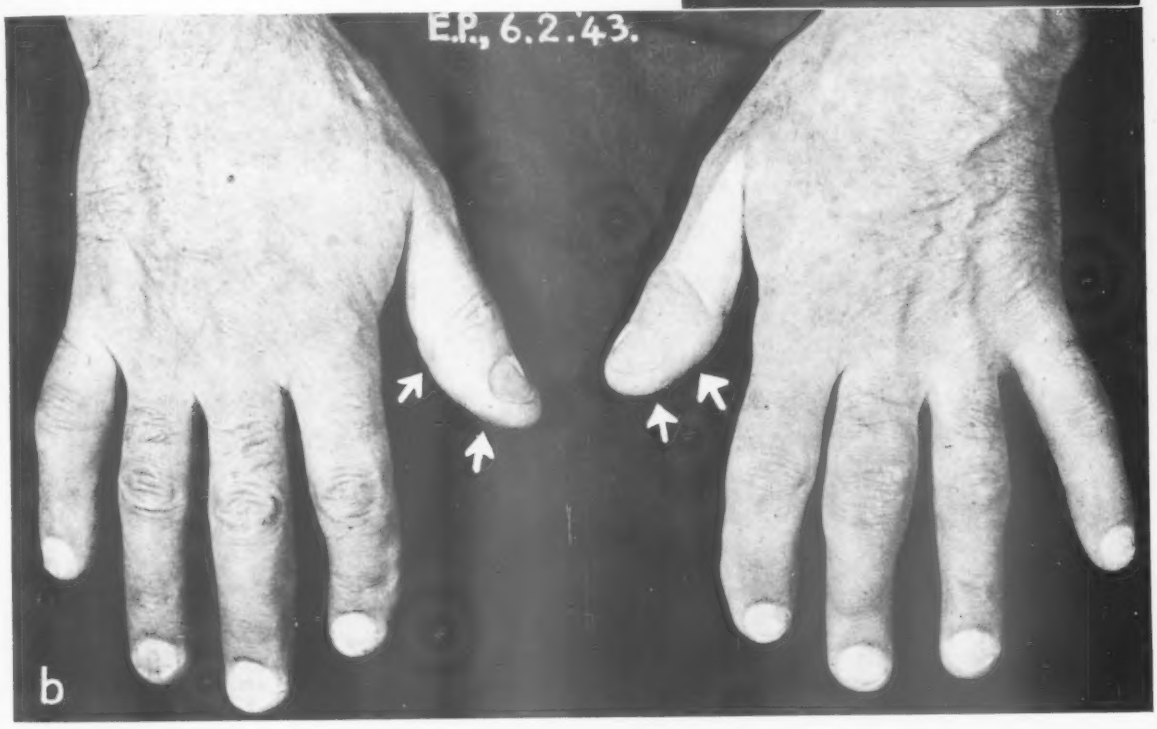


FIG. 1.—Case 1. (a) Left elbow showing subcutaneous nodule. (b) Hands showing swelling of proximal interphalangeal joints (right fifth; left fifth, third, and second), and sites of cutaneous nodules in digital pads of the thumbs (arrows).



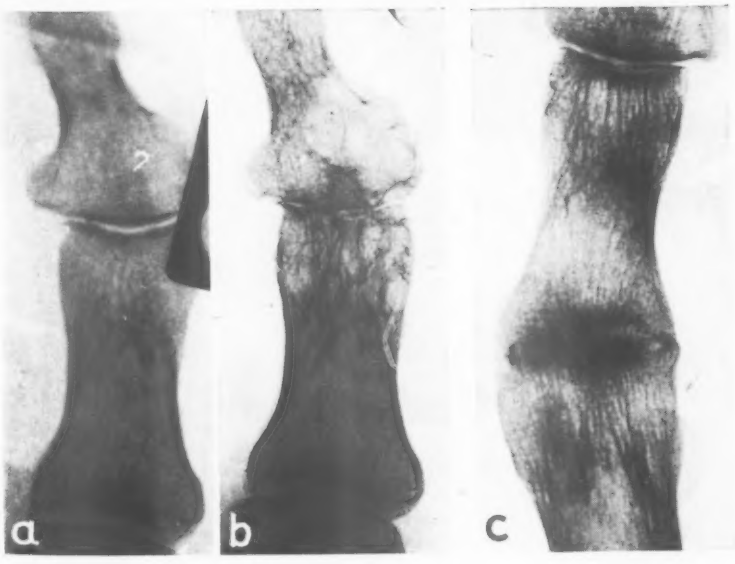
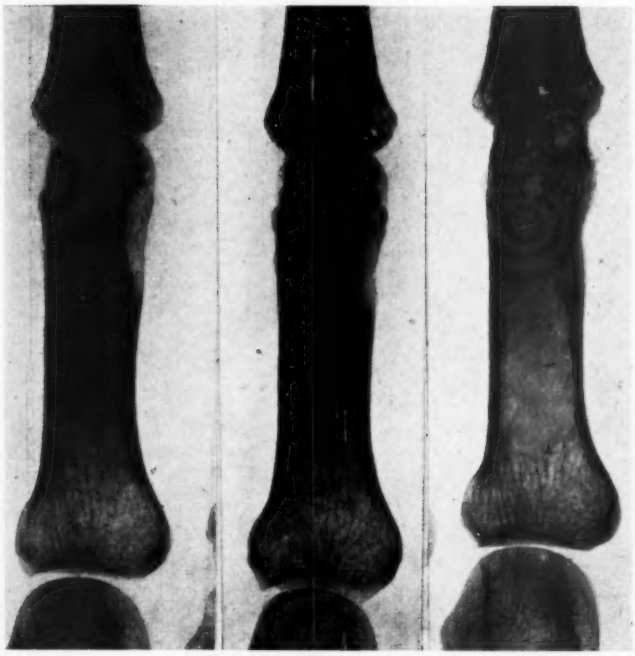
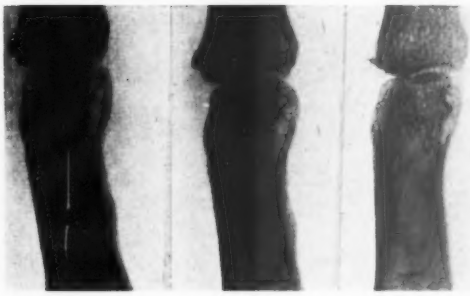


FIG. 2.—Case 1. Radiographs of big toe joints showing development of change between Feb. 8, 1943 (a, right), and July 20, 1945 (b and c, right and left respectively).



(a)



(b)

FIG. 3.—Case 1. Radiographs showing changes in the third (a) and fifth (b) proximal phalangeal heads right hand (compare Fig. 1 (b)). Note progression of lesions from Feb. 8, 1943 (left), to May 15, 1943, and July 20, 1945 (right).

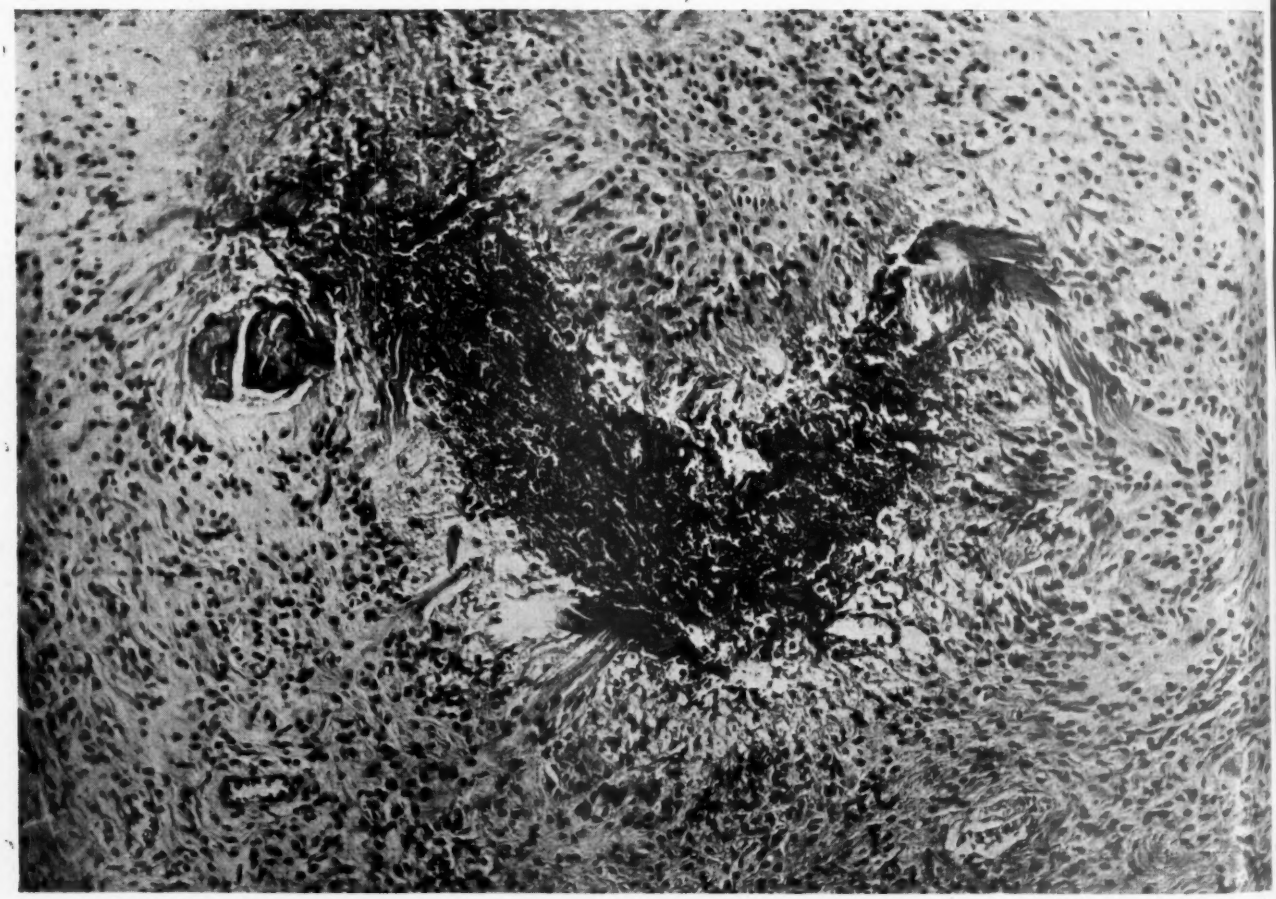
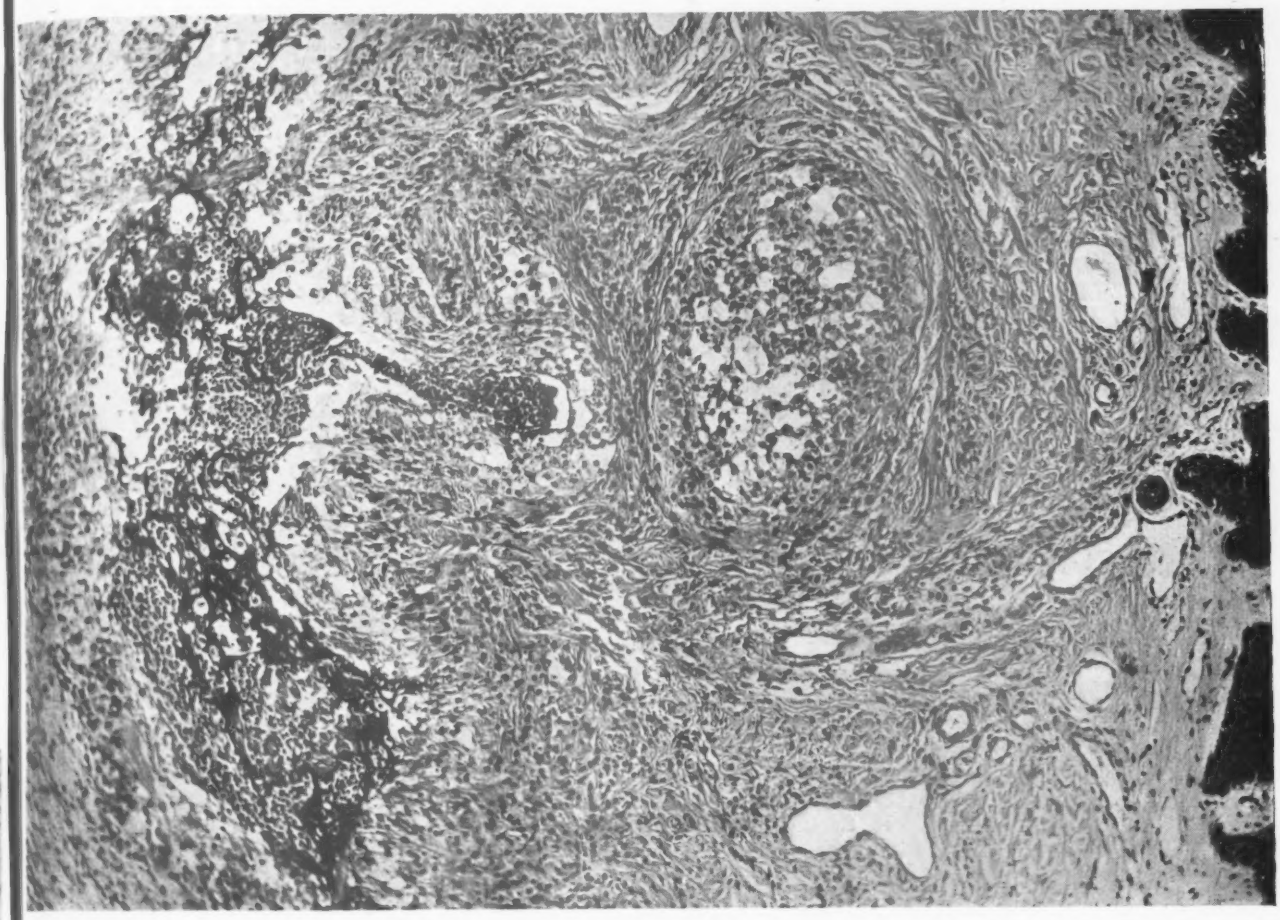


FIG. 4.—Case 1. Subcutaneous nodule from left elbow region (stained haematoxylin and eosin, × 120) showing central necrotic area with altered collagen and surrounding palisade layer undergoing vacuolation centrally.



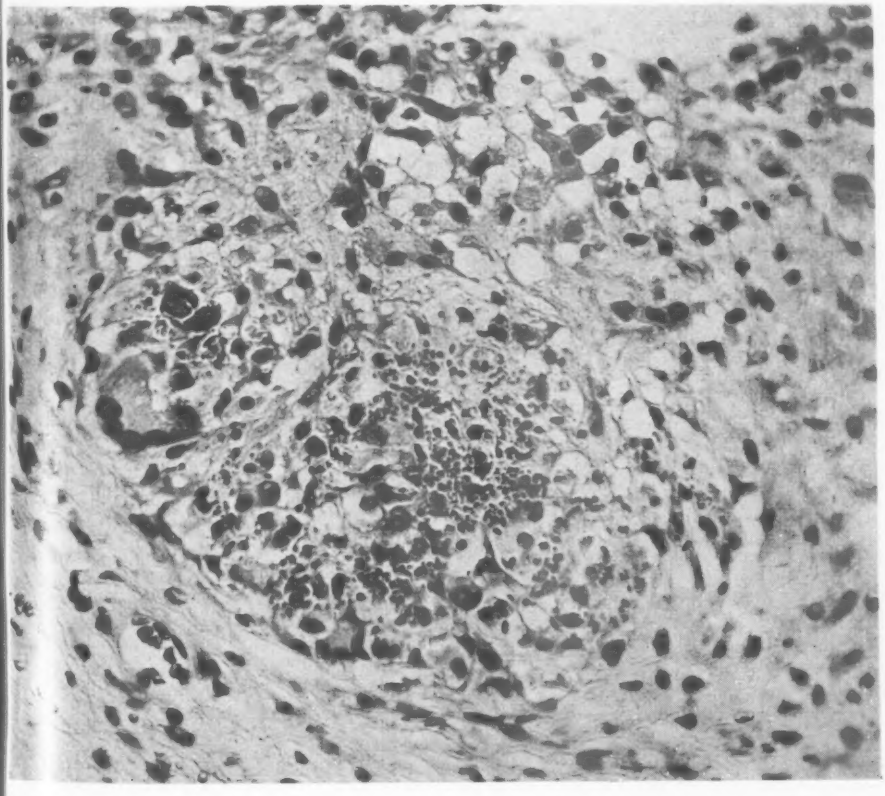


FIG. 5 (above).—Case 1. Cutaneous nodule from thumb pad (stained haematoxylin and eosin, × 90) showing necrotic collagen and fibrinoid material, basophil in character and infiltrated with pyknotic polymorphs, in central necrotic area. This is surrounded by a palisade layer, showing hydropic vacuolation in places. Superficial to this is a histiocyte nest in an earlier stage of development. (Epidermis on the right.)

FIG. 6 (left).—Case 1. Synovial membrane from finger cyst (third proximal interphalangeal) (stained haematoxylin and eosin, × 300) showing nest of refractile eosinophil bodies with giant cells of foreign-body type.

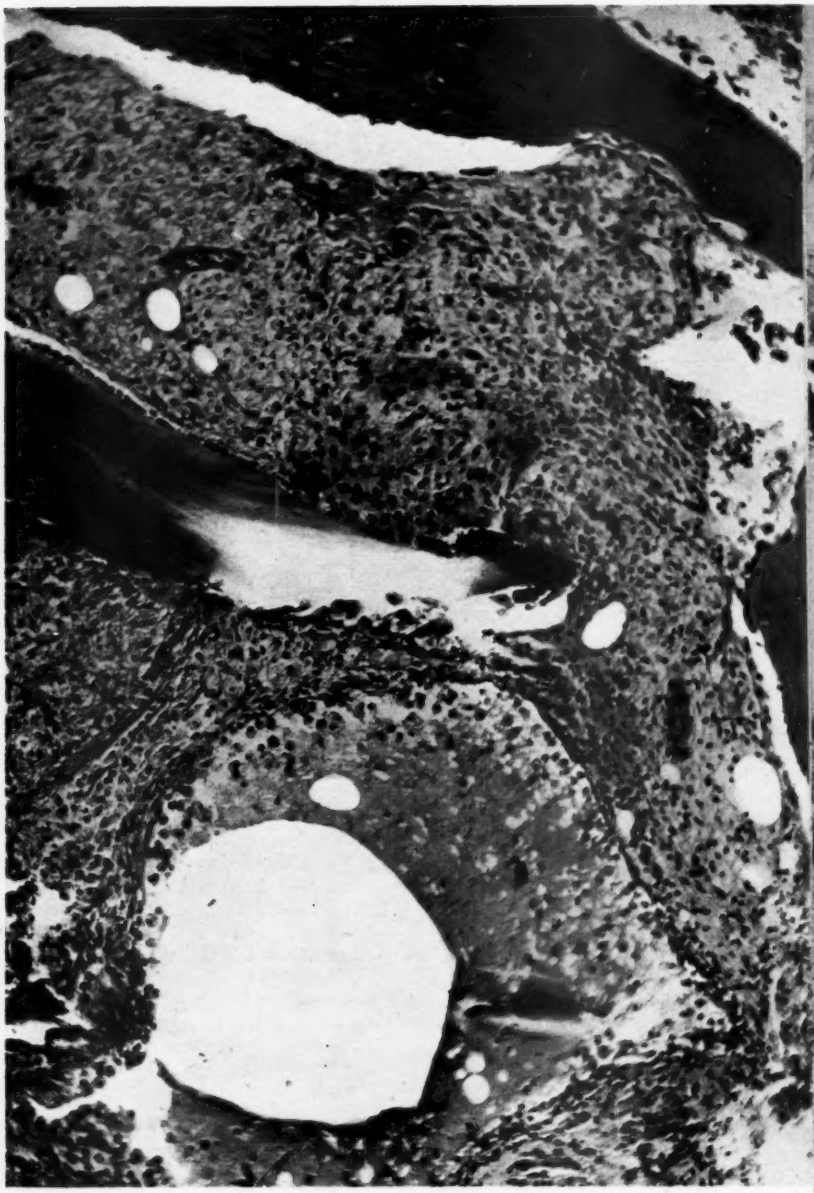


FIG. 7.—Case 1. Bone (stained haematoxylin and eosin, × 115) adjoining third proximal interphalangeal joint showing cyst, replacement of marrow by fibrous tissue, and foam cells with osteoclastic resorption of bone.

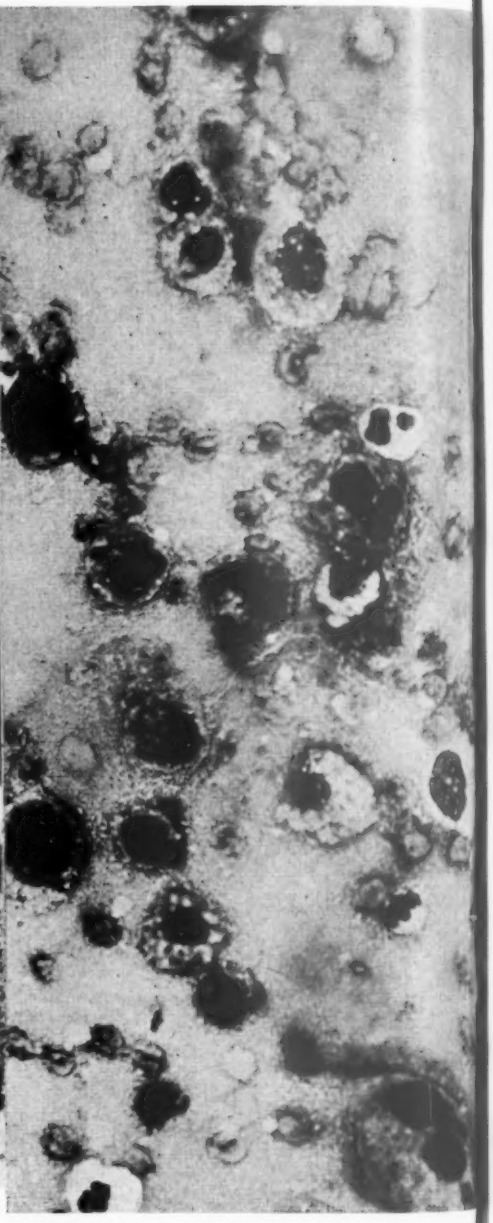


FIG. 8.—Case 1. Exudate (Leishman, × 500) from finger cyst showing macrophages.

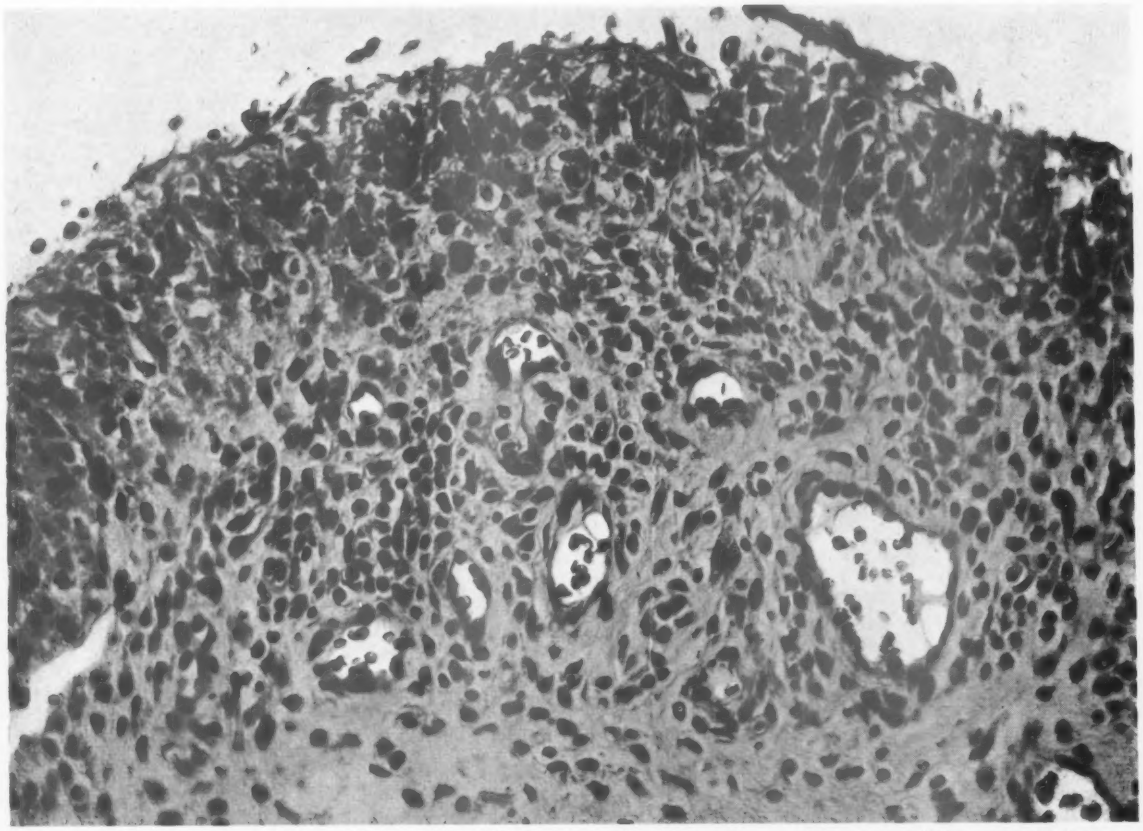


FIG. 9.—Case 1. Synovial membrane (stained haematoxylin and eosin, × 280) from fifth proximal interphalangeal joint showing hypertrophy of lining cells with fibrin exudate and perivascular polymorph infiltration subjacent to that.

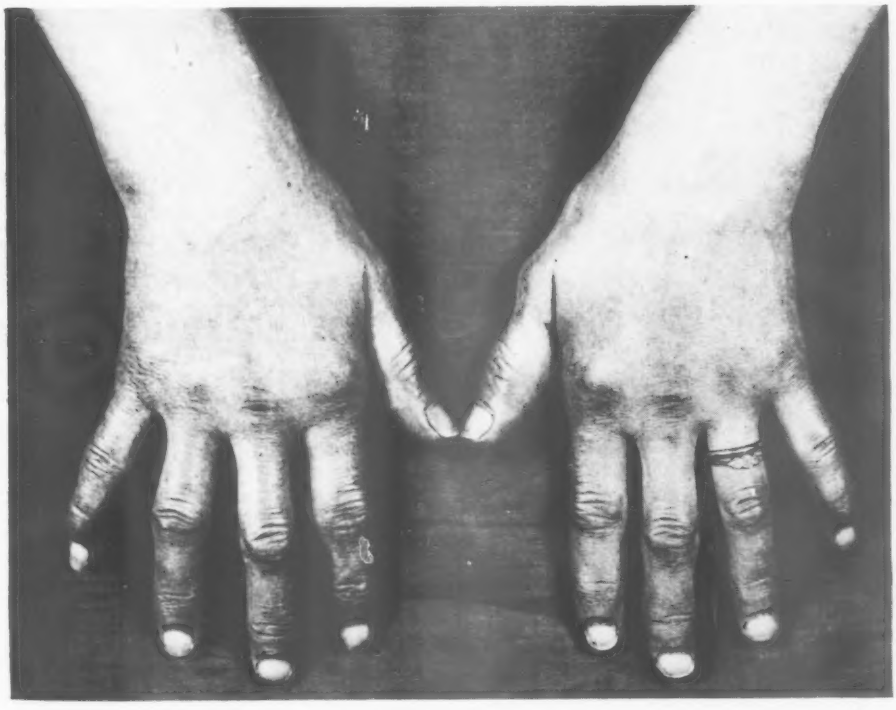


FIG. 10.—Case 2. Dorsal view of hands to show erythema, joint swellings, nail bed thromboses, and cutaneous nodules.

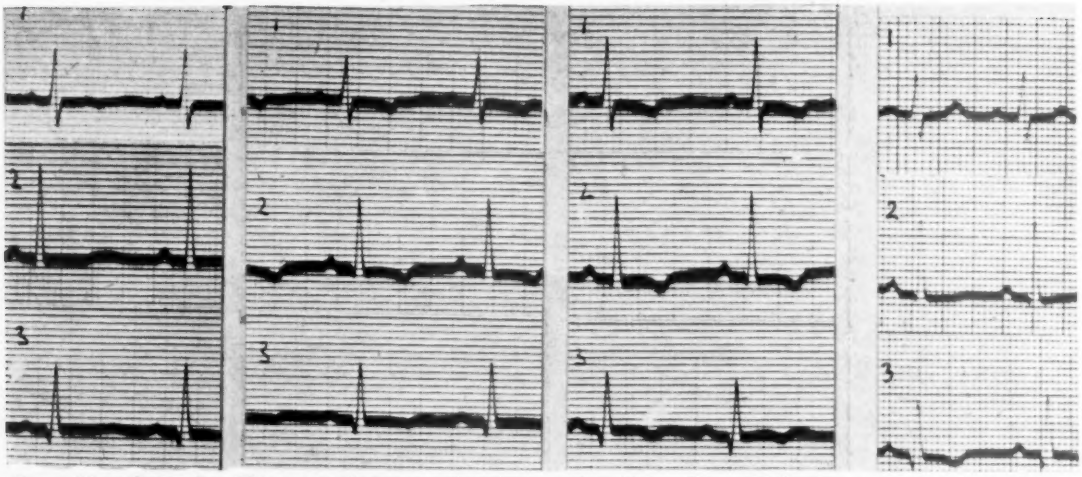


FIG. 11.—Case 2. Electrocardiogram showing pericarditis. The cardiograms were taken, from left to right, on May 17, May 30, and June 8, 1946, and on Feb. 5, 1947.

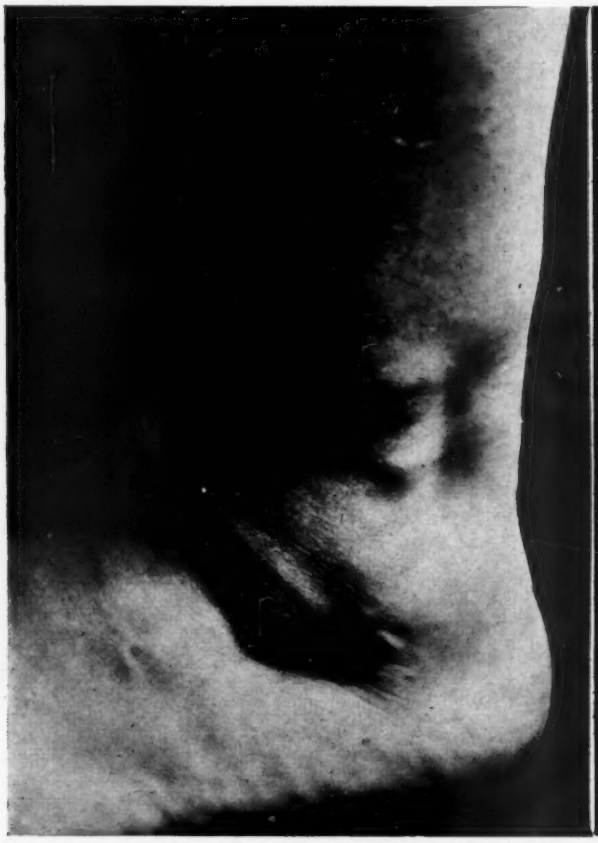


FIG. 13.—Case 2. Subcutaneous nodules over Achilles and peroneal tendons.

FIG. 14.—Case 2. Left hand to show palmar contracture and flexion of three medial fingers.

FIG. 12.—Case 2. Painting of right hand to show cutaneous nodules in various stages of development.

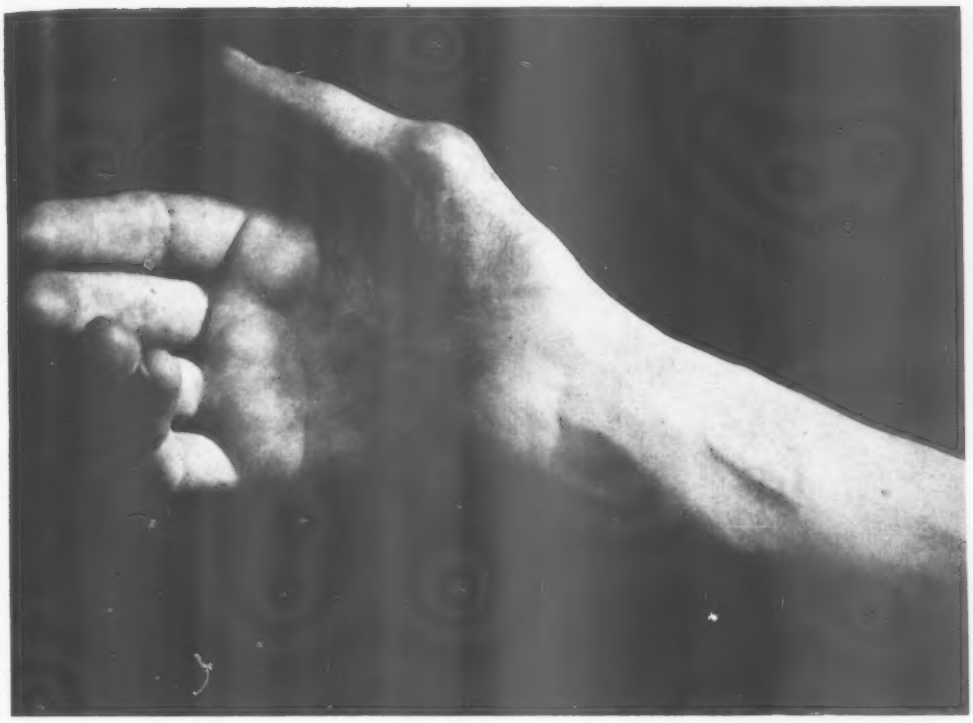


FIG. 15.—Case 2. Para-articular swelling over flexor muscle tendons with pitting oedema.

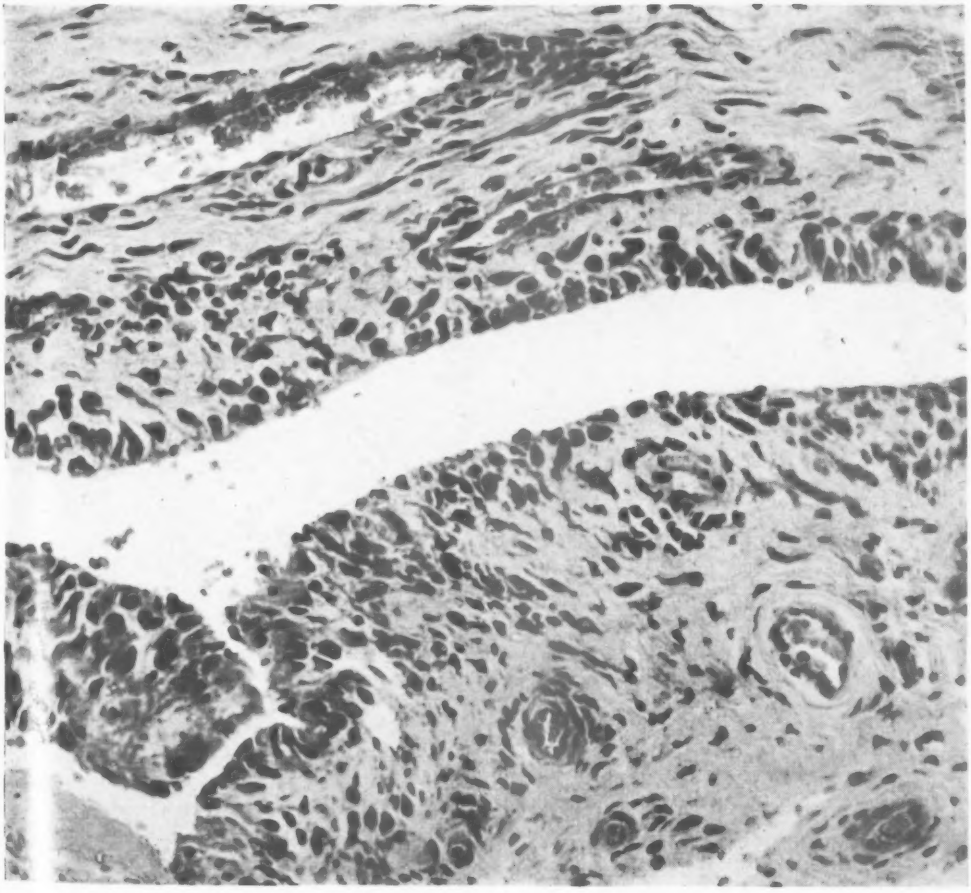


FIG. 16.—Case 2. Synovial membrane (stained haematoxylin and eosin, × 280) showing perivascular polymorph infiltration beneath hypertrophied lining membrane.

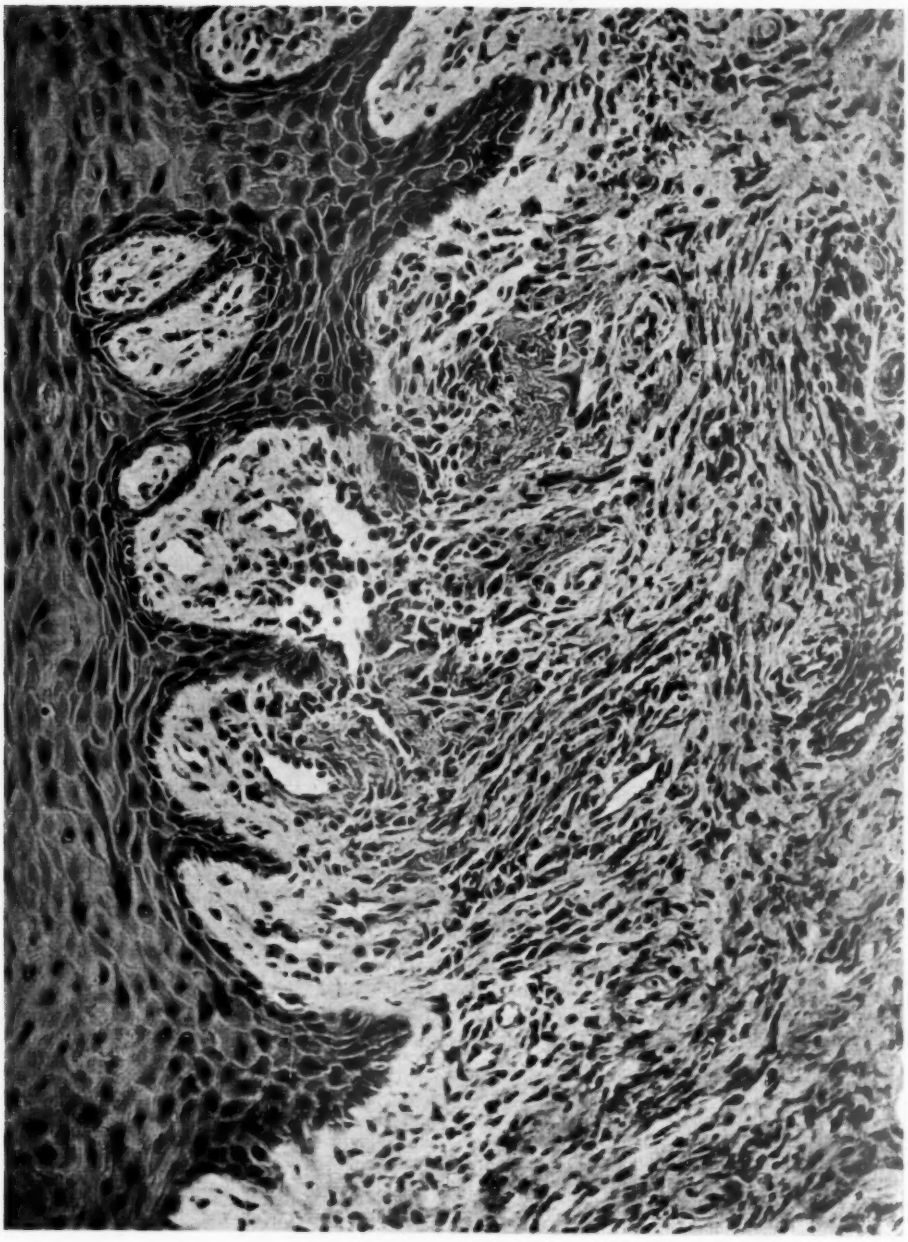


FIG. 17.—Case 2. Cutaneous nodule (stained haematoxylin and eosin, × 175) from finger pad.

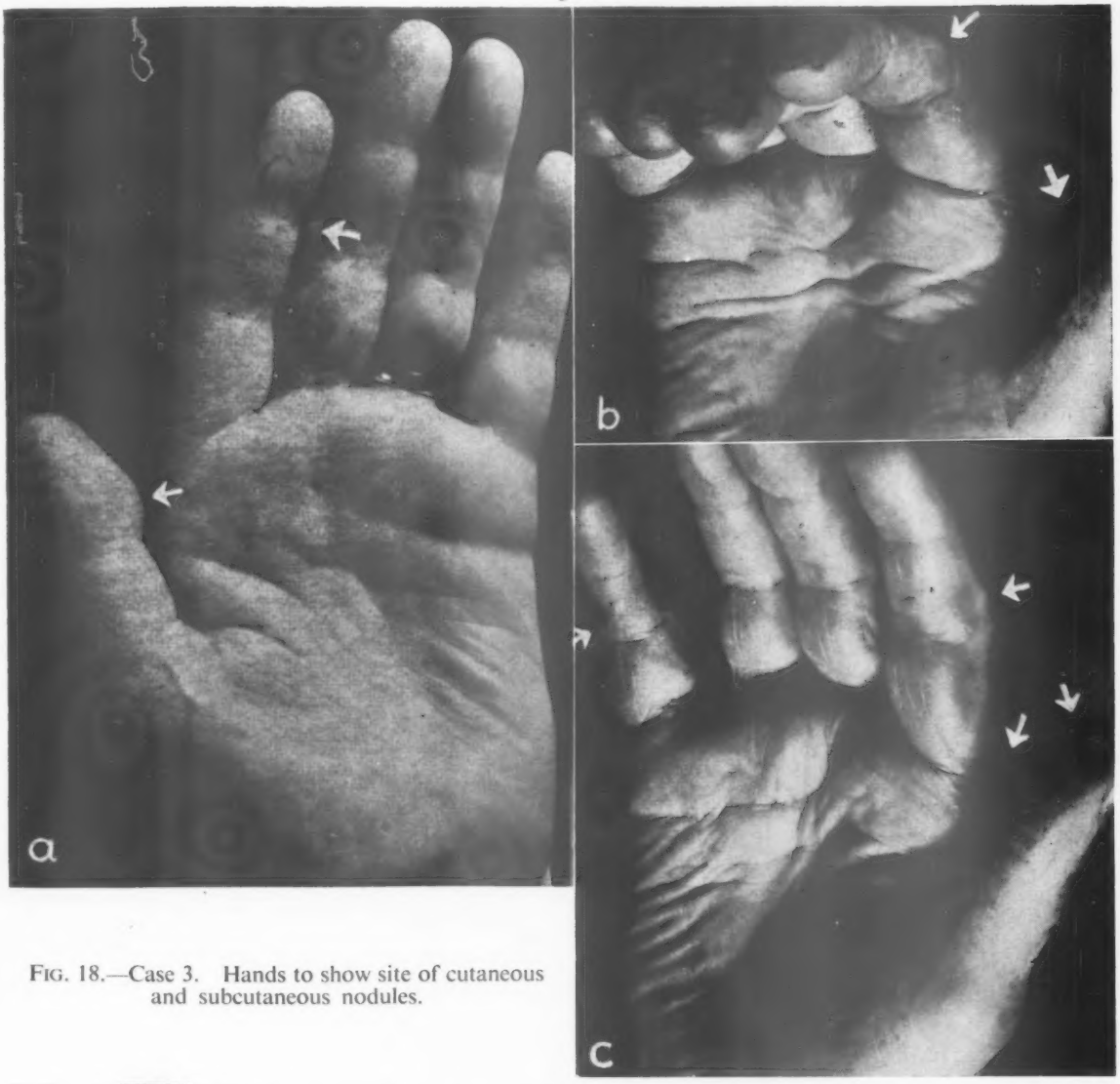


FIG. 18.—Case 3. Hands to show site of cutaneous and subcutaneous nodules.

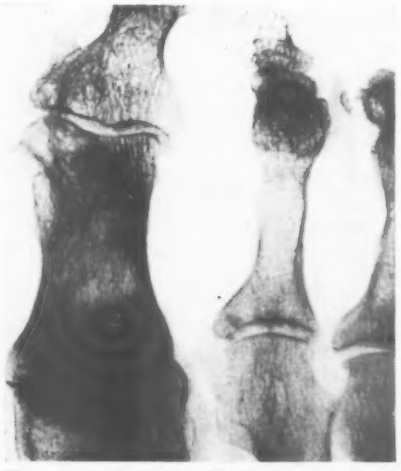


FIG. 19.—Case 3. Radiograph of big toe: note "cyst" formation and similarity to changes in Case 1.

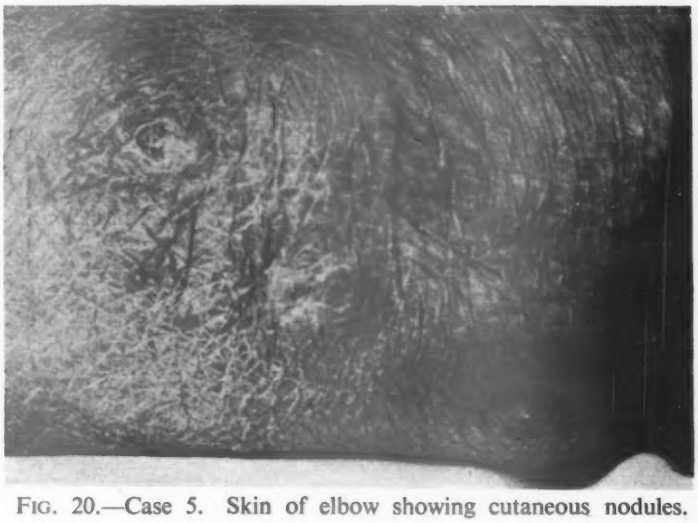


FIG. 20.—Case 5. Skin of elbow showing cutaneous nodules.

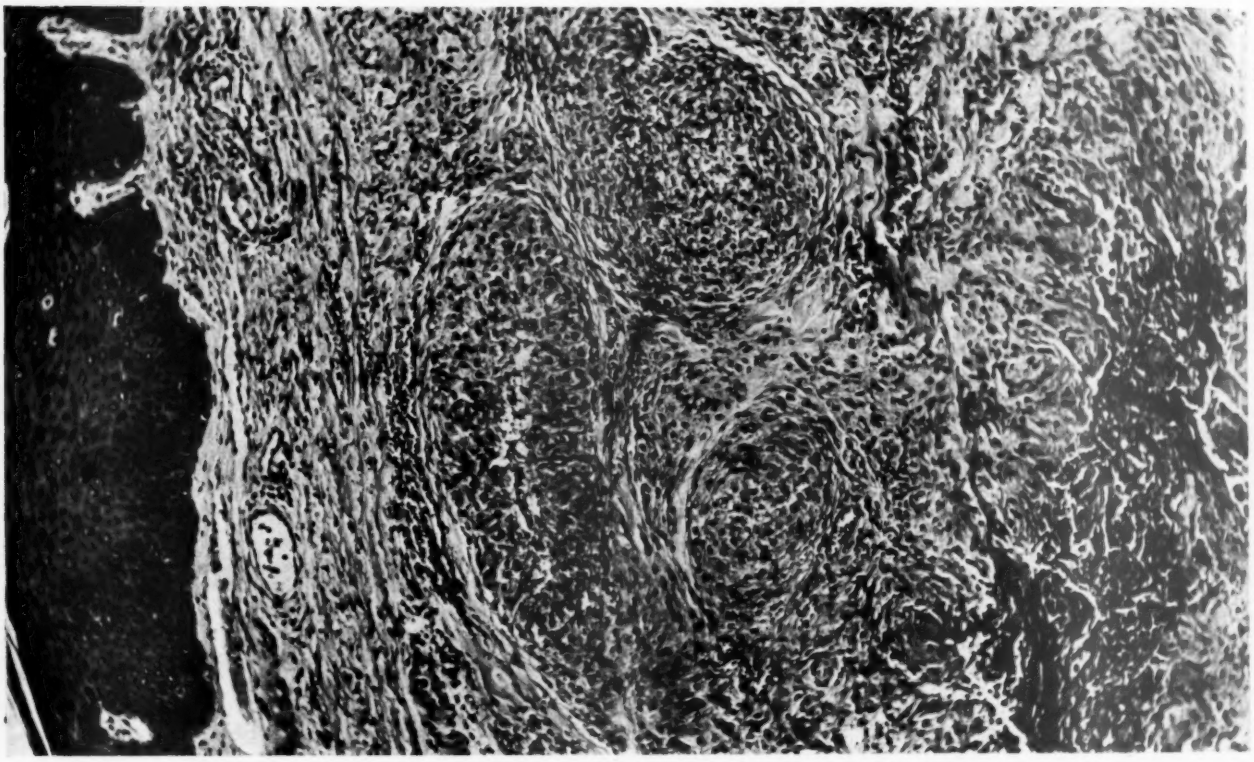


FIG. 22.—Case 5. The same, stained for reticulin (× 90).

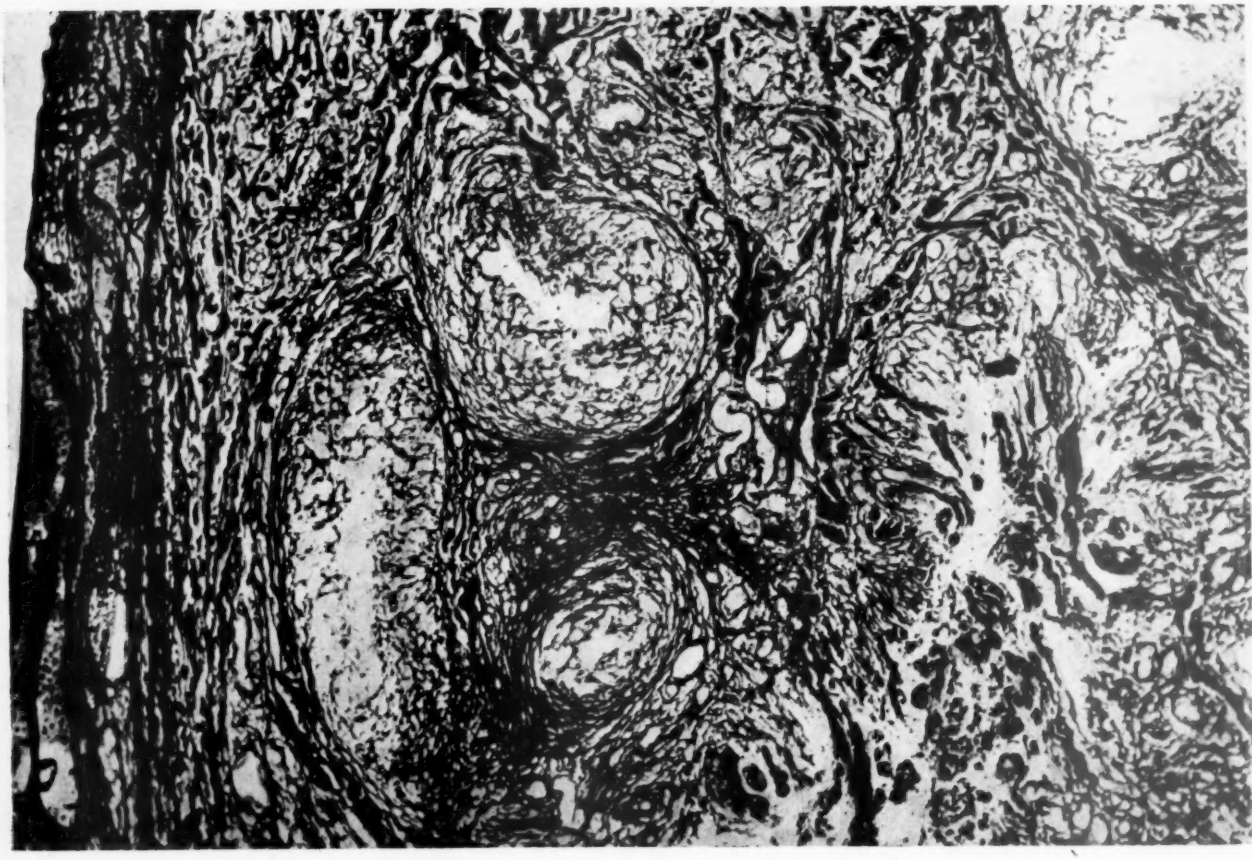


FIG. 21.—Case 5. Cutaneous nodule (stained haematoxylin and eosin, × 90) from

FIG. 21.—Case 5. Cutaneous nodule (stained haematoxylin and eosin, × 90) from

FIG. 22.—Case 5. The same, stained for reticulin (× 90).

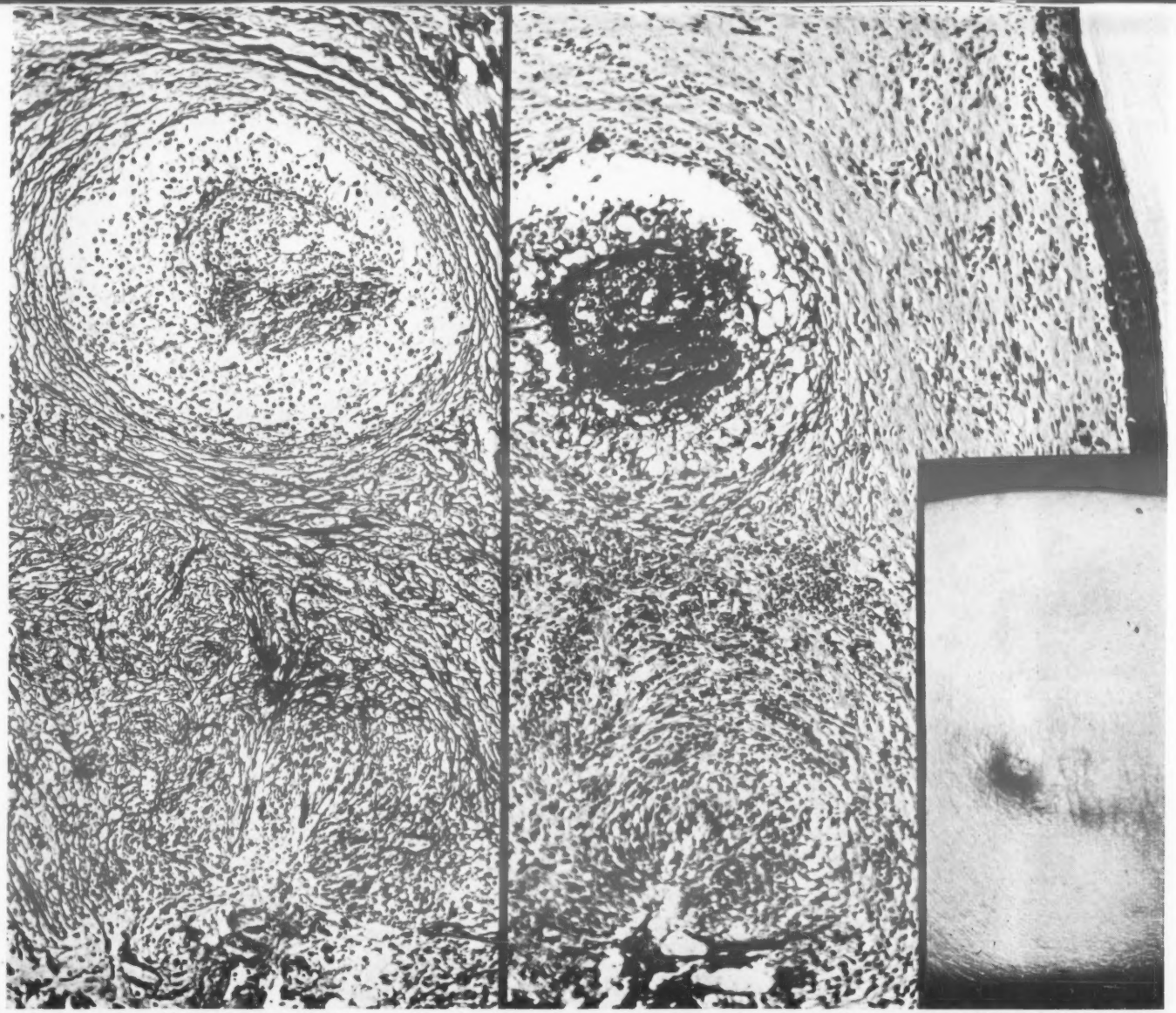


FIG. 23.—Case 6. Cutaneous nodule from elbow, with sections of same (stained haematoxylin and eosin (right), and reticulin (left)). Note, below, "necrobiosis": above, histiocyte nest with only slight reticulin development. × 90

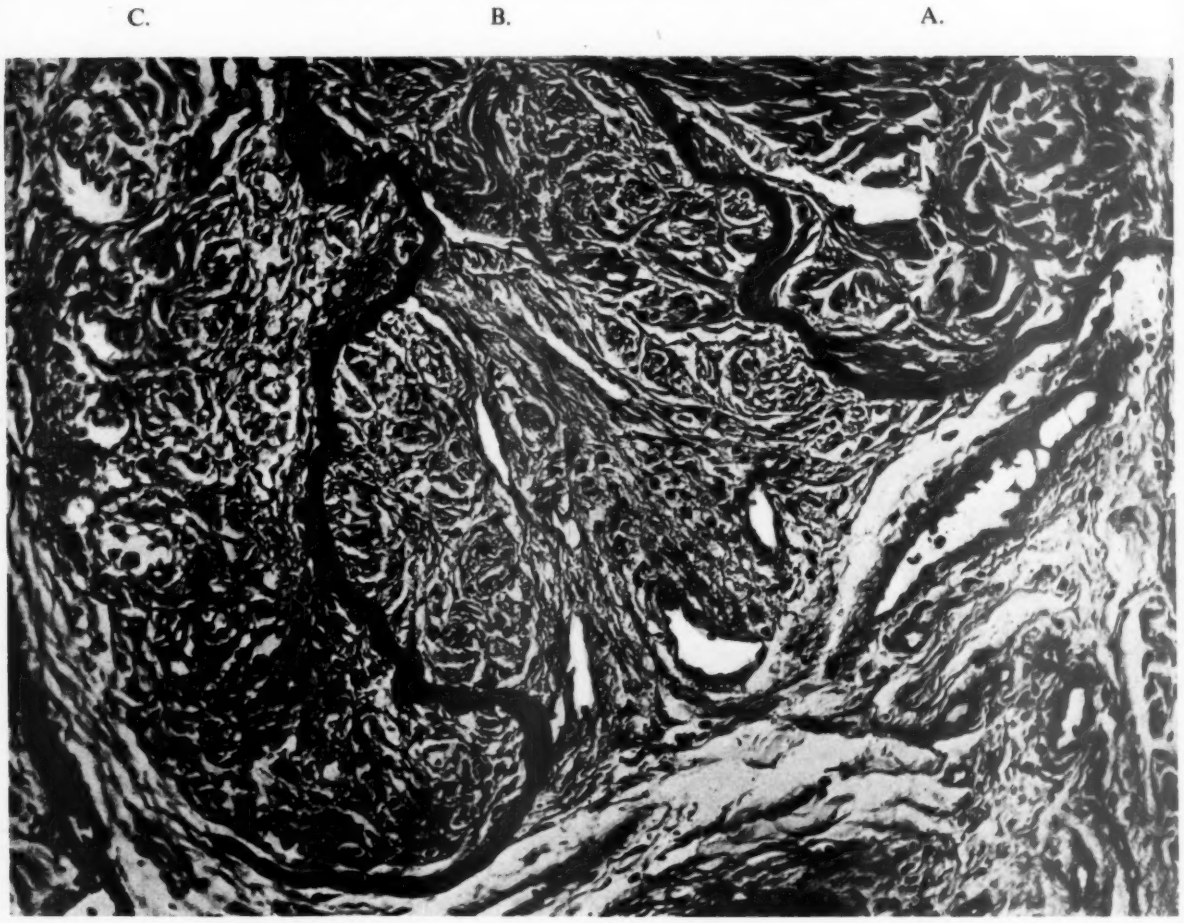


FIG. 24.—Case 1. Presumed early stage in nodule outskirts (stained azocarmine, × 280). Note three zones: A, normal collagen; B, collagen bundles separated into fibrillae; C, zone of cellular infiltration and degeneration of collagen. (Zone boundaries drawn in.)

of the nodule, the scab of which finally desquamated, leaving a small scarred area, slightly depressed and characteristically pigmented, the pigmented patch being about 1 mm. across. They were sore for the first day or two only, then the scab formed and desquamated in about four days or longer. A few appeared occasionally on the dorsum of the terminal phalanx of the index finger, but, as a rule they affected the pads of the thumb and index fingers, only rarely appearing on the third and fourth fingers. None was seen on the fifth finger. At the time of writing these skin nodules are still occurring on the digits, chiefly on the terminal pads but also on the more proximal flexor pressure pads. At one time (May 18, 1948) twenty-seven cutaneous lesions in various phases of development or involution were counted on the palmar aspect of the fingers and thumbs. Two of them were biopsied (see below).

More ordinary subcutaneous rheumatoid nodules of a larger size (10 to 30 mm. across) appeared gradually during this time on both elbows, over the sacrum, over the dorsum of the fourth and fifth right proximal interphalangeal joints, over the left ulnar-styloid process, over the third right metacarpo-phalangeal joint, over both Achilles tendons, and in the sheath of the left peronei (see Fig. 13). There were also similar nodules apparently in the sheath of the left long thumb extensor tendons and a nodular thickening in the main bulk of the extensor muscles below the left elbow. These nodules were permanent and both clinically and histologically differed in no way from the ordinary subcutaneous nodule of rheumatoid arthritis. Cystic change occurred in one of the olecranal nodules, later biopsied.

Towards the end of the first week in hospital an indurated swelling appeared in the palm of the right hand, affecting the aponeurosis of the second, fourth, and fifth fingers, which were contracted as in Dupuytren's contracture and could be neither passively or actively extended (Fig. 14). This lasted two days only and then completely disappeared to be followed by a similar condition in the palm of the left hand affecting the third finger. Recurrences were noted a week later affecting the right third and fourth fingers for a few days, and several times

since then. They came on very suddenly, in eight hours, and were thought to be due to involvement of the palmar fasciae, since the contraction involved the proximal interphalangeal joint mostly. According to the patient, these were also brought on by local trauma, such as, on one occasion, that involved in peeling apples.

Tenosynovitis with effusion was noticed on many occasions, both with and without crepitus, involving the right or left flexor longus pollicis, the carpi radialis, and the long thumb extensor sheaths, and lasting for about two or three days only. The swelling was tender for the first day and usually involved one forearm only at a time, recurring every few weeks. Other transient periarticular swellings were noticed from time to time over the dorsal aspect of the carpus and over the ventral aspect of the forearm proximal to the wrist (Fig. 15) lasting a few days and occasionally pitting on pressure. The left upper forearm was the seat of a recurrent hot red brawny swelling without nodularity involving the whole flexor surface, unassociated with effusion of the elbow joint and lasting about a week at a time, possibly due to inflammation of the fasciae between the flexor muscles.

The joints themselves showed the same recurrent pattern, shoulders and knees being affected most, wrists, finger joints, ankles, elbows, and metatarso-phalangeal joints next. While the knees showed effusions at all times, this was variable in content, but the finger joints became gradually more swollen; effusions were palpable in right second, third, fourth and fifth, and left second, third and fifth metacarpo-phalangeal joints, in right second and third and the left second, third and fifth PIP joints, and in both first carpo-metacarpal joints. These stayed swollen, and the hand grip was decreased to about one fifth of normal, more so in the right than in the left hand, probably due to the greater involvement and limitation of the right wrist (for example, 17 cm. Hg. left, 1 cm., Hg. right, compared with 50 or 60 cm. for an average normal female). Raynaud-like phenomena were marked in cold weather. Biopsy of one affected metacarpo-phalangeal joint and of the olecranal nodule showed changes consistent with a diagnosis of rheumatoid arthritis (Fig. 16). A digital pad nodule was also biopsied (Fig. 17).

From August 1946, following a sore throat, she lost her voice and could talk only in a husky whisper: this lasted with occasional intermissions for over a year.

Treatment during this time, consisting of heat, active and passive movements, exercises, splints, and salicylates, gave no more than symptomatic relief. The sedimentation rate, 43 mm. per hour (Westergren) on admission, fell gradually to 20 and stayed between 20 and 35 mm. during the next two years. The antistreptolysin titre was 160 units per ml.; colloidal gold 5 units. On several occasions the white count was low, reaching 3,000 per c.mm. with 33 per cent. polymorphs on one occasion, and, together with the serositis, joint effusions, albuminuria, and facial rash suggesting lupus erythematosus of the subacute disseminated or visceral type. No really characteristic rash or subsequent atrophy was, however, seen.

Summary.—The patient showed changes distinctly resembling rheumatoid arthritis but of an acute and recurrent type, associated with pericarditis, tenosynovitis, fasciitis, and nodules, both in and beneath the skin. There was also a facial rash, leukopenia, fever, and transient albuminuria.

Comment.—This case showed well the nature of the stimuli producing nodules in the finger pads. They were produced by pressure due to household duties and experimentally by pencil-point pressure. Other points of interest were the hoarseness, the marked flushing of the butterfly area of the face (recalling the rash of lupus erythematosus), and the flushing of the palms seen so frequently in rheumatoid arthritis and also in pregnancy, diseases of the liver, etc. The pericarditis again points to the acuteness of the condition. While a few cases of rheumatoid arthritis and particularly of Still's disease, can be shown at necropsy to have had pericarditis, this is not a frequent finding and, in fact, was picked up here first from the electrocardiogram. It seems possible that more frequent electrocardiogram records might display this picture in other cases.

Three other cases will be recorded more briefly.

Case 3

R.H., a woman aged 57, at the time of her first admission to hospital (Feb. 6, 1943) had previously been in good health (except for typhoid fever at the age of 16) until five years after the menopause which occurred at the age of 50. Her feet then became painful and swollen, after which the hands and knees became involved. She had been in bed for four months prior to admission.

One of her brothers had a similar illness, and another was said to have died of it.

Examination.—The hands showed involvement of the left and right second metacarpal, the right fourth and left second PIP joints of both wrists: there was interosseous wasting and ulnar deviation. Both knees and ankles were swollen and showed slight limitation. General physical examination showed no noteworthy abnormality. She was afebrile; the sedimentation rate was 70 mm. in one hour (Westergren). The haemoglobin was 10·6 g. per cent. *X*-ray examination showed rarefaction and loss of cartilage in the right knee and left wrist and carpus. She was transferred to another hospital where a course of gold therapy was given. Nodules appeared on the left elbow a year later and on the right elbow three years later, just prior to her second admission (June 10, 1946).

From about February 1946 she had a continuous series of small nodules on the fingers of both hands, generally following use of the household broom. They lasted for a few days up to two weeks or longer and then if the patient abstained from work tended to disappear. They

were very painful "as if festering" during the early stages of development and made it difficult for her to pick things up.

Examination showed the characteristic changes of rheumatoid arthritis in the various joints affected. Classical nodules were present over both ulnar crests and over the long extensor tendons of the toes above the ankle. Small cutaneous nodules about 5 mm. in diameter, cystic on palpation, were present in the digital pads of both thumbs and of the second and third fingers of the right hand, and along the grip contact areas of both thumbs, of the right index finger and the right fifth finger (Fig. 18). Her grip was weak (4 cm., right, and 2 cm. Hg, left), compared with a normal female grip of 50 to 60). There was also a transient contraction of the palmar fascia of both hands, involving the skin and limiting full extension of the second and third right fingers, which disappeared a week later. Later the usual fixed palmar contracture occurred, complicated occasionally by sticking of the fourth finger in flexion for a few minutes such as might be produced by a swollen tendon or a shrunken sheath.

Investigations.—Haemoglobin was 15·1 g. per cent. M.C.H. 31; white blood cells numbered 3,400 per c.mm. of blood, 63 per cent. polymorphs. The Wassermann reaction was negative, the electrocardiogram normal; there was no urine abnormality. The sedimentation rate was 46 mm. in one hour, rising later to 70 and 92. Biopsy of the elbow nodule and of one of the dorsolateral digital nodes of the grip contact area showed, in the former, the characteristic histological picture of rheumatoid arthritis with central necrosis and a well-marked palisade layer. The latter nodule was more richly cellular and showed a fibrinoid latticework with necrosis and infiltration with polymorphs. A radiograph now showed complete loss of cartilage in both knees, both wrists, and the carpal joints with erosions in the first, second, third, fourth and fifth left, and the first, second, and third right metacarpo-phalangeal joints. The terminal big toe joints showed changes similar to but at an earlier stage than in Case 1 (Fig. 19).

Summary.—This patient had classical rheumatoid arthritis, and in addition digital pad nodules related to pressure and transient palmar contractures.

Case 4

I.M. A woman aged 28 developed alopecia totalis at the age of 15, associated with a marked depressional neurosis. At the age of 24 subtotal thyroidectomy was performed, but it is improbable that she had Graves's disease: there are now no residual signs.

Rheumatoid arthritis started at the age of 22 in the fourth month of her first pregnancy, and involved hands, knees, and feet. She now shows rheumatoid involvement of hands, feet, and knees with ulnar deviation and effusions. There is radiological bony involvement of carpus, metacarpals, and metatarsals. Urine, electrocardiogram, and blood count are normal. The erythrocyte sedimentation rate is 6 and 7 mm. in one hour (Westergren). Cholesterol is 210 mg. per cent., and the basal metabolic rate +5 to 10 per cent. She has developed a number of cutaneous nodules, usually following the use of the household broom, on the dorsal and contiguous surfaces of the thumb, index, and fifth finger joints, but has had no palmar contractures and no finger pad nodules. Biopsy shows characteristic rheumatoid granulomata.

Case 5

S.C., a woman aged 75, had had rheumatoid arthritis for twenty-nine years: it seemed now quiescent but had left her completely crippled, bedridden, and dependent on others for all the offices of life. Radiologically the hands showed typical carpal and metacarpal changes. She died of uraemia due to hydronephrosis. At necropsy both elbow regions showed many small cutaneous and subcutaneous nodules (Fig. 20); histologically they resembled closely the atypical digital pad nodule of Case 1 (Figs. 21 and 22).

Case 6

F.G., a woman aged 47, has been followed for over ten years in this clinic. She had had typical deforming rheumatoid arthritis showing radiological changes and a raised blood sedimentation rate. She developed subcutaneous nodules (typical microscopically) and after fourteen years of arthritis one *cutaneous* nodule on the elbow. This showed on section the same picture as in Cases 1 and 5 (Fig. 23).

Histological Changes

In Synovial Membrane.—Synovial membrane in Case 2 (Fig. 16) differed little from that seen in ordinary acute cases of rheumatoid arthritis: note that polymorphs rather than lymphocytes predominate. Case 1, however, showed more marked differences, resembling in several particulars those changes described by Hench and others as characteristic of palindromic rheumatism. The synovial lining cells were hypertrophic and arranged in a palisade layer. The surface was often covered with fibrin, which might be incorporated in the lining layer: these changes are common to a number of chronic synovial conditions, including tuberculosis and rheumatoid arthritis, and are seen in Hench's illustrations. The underlying connective tissue, however, contained many inflammatory cells, often surrounding dilated superficial capillaries, and consisting largely of polymorphonuclears (Fig. 9). In the chronic stage of rheumatoid arthritis, even in the not infrequent absence of lymph follicles, the cellular infiltrate consists predominantly of lymphocytes and plasma cells: polymorphonuclears are relatively less frequent, despite their marked preponderance in the synovial fluid, a fact which has never been adequately accounted for. In Hench's biopsies from cases of palindromic rheumatism the predominant cell was the polymorphonuclear leucocyte.

Other changes noted in Case 1 are the presence of fragmented granules (? collagen), (Fig. 6) and of cartilage detritus undergoing absorption, as is seen in rheumatoid arthritis. Thus, by histological criteria also, this case presents articular features resembling both rheumatoid arthritis and palindromic rheumatism.

Nodules.—Subcutaneous nodules removed from these patients were not markedly different from those encountered in classical rheumatoid arthritis (Fig. 4). In Case 1 they were perhaps rather acute in that no large amount of necrosis had occurred: in Case 2 rapid progression led to the incorporation of recognizable adipose tissue within the central necrotic area, and some increased oedema in the outer zones. Case 3 showed a well-marked ancient lesion with large necrotic zone and well-organized palisade layer.

The cutaneous nodules from the lateral aspects of the fingers of Cases 3 and 4 differed scarcely at all from the above description. Cases 1, 5, and 6 showed a different and almost identical histological picture (Figs 5, 21, and 23), although the Case 1 biopsy was of a digital pad nodule and the biopsies of Cases 5 and 6 from the elbows of old rheumatoid patients. Beneath the epidermis, nests of proliferating cells were seen, some in mitosis, sometimes becoming vacuolated towards their centre, some containing a few multinucleated giant cells. These were grouped around the periphery of deeper seated but still cutaneous nodules. The latter showed fibrinoid centres containing necrotic collagen fibres and pyknotic cells, mainly polymorphonuclear, although these cells were only rarely seen in the palisade and outer zones. The palisade layer was very thick and consisted of many layers of cells becoming vacuolated towards the necrotic zone and containing fat droplets: giant cells of foreign-body type were seen occasionally in it: it was bounded on the outer side by a peripheral skin of fibrous tissue. This palisade layer seemed to be a later and larger development of the nests, in which the centre portion had undergone necrosis. On the outskirts of the nodule, lobulated areas were seen where slightly oedematous and frayed bundles of altered collagen fibres were being invaded by dark staining macrophages (Fig. 24). This was apparently the first stage of nodule formation, since all stages therefrom towards the fully developed lesion were seen. A similar early stage is seen also in granuloma annulare, mostly in the cutaneous collagen bundles—and is a common finding in the acute rheumatic fever nodule. Reticulin stains showed the presence of altered (black-staining rather than brown-staining) argyrophil fibres in the middle of the necrotic areas, indicating the incorporation of larger collagen fibres in the undigested state: the nests of proliferating histiocytes seen in the cutis showed a few very fine new fibres, indicating that these areas form by cell proliferation (Fig. 23); if transformation of existing collagen occurs it is a very complete digestion. Thus the sequence we posit is (a) collagen alteration, (b) cellular infiltration, (c) nest formation, (d) central necrosis. Whether the initial change is in collagen or in the ground substance with secondary collagen changes we cannot say. This slightly different picture in the skin nodules compared with the subcutaneous ones is thought to be dependent on their superficial localization and hence earlier biopsy, as well as on the different pattern of collagen and ground substance therein: again it is to be emphasized that the digital pad nodules of our palindromic-like case (Case 1) were identical with cutaneous nodules from the elbows of old and deformed rheumatoid cases.

A unique picture was seen in the two digital pad nodules removed from Case 2 (Fig. 17). Immediately beneath the basal cell layer a collection of histiocytes, plasma cells, and lymphocytes was seen surrounding small amorphous hyaline masses staining lightly with eosin. The keratin layer was thickened and showed blister formation over the central infiltrated area: vessels in the neighbourhood showed a few histiocytes and lymphocytes around them. These were ancient resolving lesions, having been present for several weeks. They could be described as miliary rheumatoid nodules.

Discussion

Cutaneous Nodules.—Only rarely is it difficult to distinguish histologically between the subcutaneous nodules of rheumatic fever and those of rheumatoid arthritis (Bennett and others, 1940). All our cases showed true rheumatoid nodules; they could be distinguished (but with some difficulty) from the rare subcutaneous nodule (see Gray, 1914; Goldschmidt, 1925; Grauer, 1934), of granuloma annulare, as seen in the four cases of that condition that we have biopsied. The nodules of necrobiosis lipoidica diabeticorum also resemble closely the lesions of granuloma annulare, as Ellis and Kirby Smith have shown: since 10 per cent. (Goldberg, 1943) to 30 per cent. (Ellis and Kirby Smith, 1942) of patients with this lesion are not diabetic, the distinction, both clinical and pathological, if it is a real one, may be difficult.

The fibrous nodules on extensor surfaces recorded in primary diffuse atrophy or acrodermatitis chronica atrophicans (Herxheimer and Hartmann, 1902) are said to resemble the rheumatoid nodule,

but as Sweitzer and Laymon, 1935, Jessner and Lowenstamm, 1924, and Hövelborn, 1931, include typical cases of rheumatoid arthritis with skin atrophy in this category, some such fibrous nodules (situated as a rule over the subcutaneous ulna bone—" ulnar bands ") may indeed be merely rheumatoid. Others may be of the type associated with scleroderma (Gray, 1923; Fletcher, 1921), since many of the acrodermatitis chronica atrophicans cases are recorded as showing sclerodermatous change (compare Jessner and Lowenstamm, 1924, and Sweitzer and Laymon, 1935).

We have had no experience of the juxta-articular nodes of syphilis and allied infections (Hopkins, 1931), but from the excellent pathological description of Tuta and Coombs (1942), differentiation should be very easy.

If we eliminate the occasionally seen ulceration of subcutaneous nodules through the true skin, the existence of *cutaneous* rheumatoid nodules seems to be largely unrecognized (see Keil's (1938) complete and careful monograph on rheumatic subcutaneous nodules). There are two doubtful descriptions from the last century (Middleton, 1887; Bury, 1889), but it is difficult to classify what is described. The former concerned flattened elevations on the skin (pea to hazel-nut in size) of the pads of the fingers (illustrated), adherent to the skin but not to deeper structures and accompanied by other subcutaneous nodules on knuckles and tendons in a woman of 39 years who had had acute rheumatism aged 13 and 36 years with, between, frequent pain and swelling in various joints. Biopsy showed inflammatory cells and blood vessels but the histology is not described sufficiently to be helpful.

The latter case is even less clearly defined and may well have been one of erythema elevatum diutinum. Much confusion seems to have arisen as a result of the inclusion in the original account of erythema elevatum diutinum by Crocker and Williams (1894) of Bury's case which most dermatologists believe to have been one of granuloma annulare (cutaneous type). While Graham Little originally held (1908) that erythema elevatum diutinum was a variety of granuloma annulare, a view still held by many, he and Goldsmith later thought (in a discussion of Gray's case, 1932) that erythema elevatum diutinum differed from granuloma annulare in the absence of discrete nodules: this is a view which has been championed by Combes and Bluefarb (1940), who point out that erythema elevatum diutinum is bilaterally symmetrical, whereas granuloma annulare is seldom so: it affects middle-aged and old men, as against the children and young females with granuloma annulare. It is a flat raised red plaque with no central clearing, as compared with the depressed centre and nodular periphery of granuloma annulare, and histologically it is characterized by polymorph infiltration rather than by necrosis.

It is interesting to note, however, that in the clinically typical cases of erythema elevatum diutinum described by Trimble in 1926 acute attacks of recurrent polyarthritis occurred and polymorphs were not seen in the biopsied tissue: fibrosis, round-cell infiltration, and foam cells (such as are seen in rheumatoid nodules) were noted. Similarly in both the two cases described by Weidman and Besançon (1929), acute infections and recurrent polyarthritis occurred with nodules and plaques over knuckles, elbows, etc. Biopsy showed necrosis with polymorphs in the necrotic area, and the photograph shows a cutaneous nodule closely resembling what is usually seen in granuloma annulare and not distinguishable from those described in this paper as part of the rheumatoid arthritis syndrome. The clinical description of the skin lesion is, however, very different since the plaque-like aspect was quite absent in our cases. We may conclude that the description and labelling of skin manifestations has outrun correlation with other aspects of these diseases and that the nosological status of these above-mentioned eruptions must remain for the moment undetermined.

The only paper on cutaneous nodules in rheumatism of recent years is by Rosenberg (1934), describing two cases. The first was a woman of 46 years who had had pain in her hands, wrists, and knees for seven months, and who showed on examination swelling and extreme tenderness of the interphalangeal, metacarpo-phalangeal, and carpal joints (being unable to close her fists completely) as well as in her knees and elbows. The sedimentation rate (32 mm. in one hour, Westergren), haemoglobin (77 per cent.), erythrocytes (3·8 million per c.mm. of blood), leucocytes (7,000 per c.mm.), and *x*-ray appearances (decalcification only), were all compatible with but not diagnostic of rheumatoid arthritis. She developed in the six weeks prior to admission nodules on the volar and dorsal aspects of fingers and palms, red, varying in size from a pinhead to a hazel-nut, and not painful except on firm pressure. A new crop developed prior to admission lasting one month and a third crop three months later, affecting this time the neck, forehead, and cheeks, and disappearing in one month. Biopsy showed only a few lymphocytes and plasma cells, aggregated round the cutaneous vessels. The photographs of finger, face, and biopsied nodule are unhelpful, and it is indeed difficult to

imagine what such facial nodules might be, perhaps sarcoid or erythema nodosum, which sometimes occurs on the face (Bluefarb and Morris, 1941). The second case suggests subacute bacterial endocarditis with Osler's nodes although repeated blood cultures were negative (migratory joint pain, blowing apical systolic murmurs, anaemia, slight polymorpho-leucocytosis, and septic fever for five weeks with crops of red pimples on extremities and chest, biopsy of which showed polymorphs and round cells in the walls of the cutaneous blood vessels).

In our Cases 1, 2, and 3, these digital nodules at one stage resembled clinically Osler's nodes. Often painful or, at least, tender when they first appeared, they follow closely Osler's account of Mullen's description. " Small swollen areas, some the size of a pea . . . raised red . . . near the tip of the finger which may be slightly swollen . . ." In those first seven cases the nodes were " not beneath but in the skin ", " affecting the digital pads, thenar and hypothenar eminences of the sides of the fingers " with a slightly opaque centre " in all probability caused by minute emboli " (Osler, 1908-9). Blumer (1926) remarks that such nodes " have a small brownish stain behind them and occasionally leave a small scab which may be picked off ", a description closely corresponding to the digital nodules of Case 2 in this paper. However, although Keil amongst forty-two cases of subacute bacterial endocarditis has observed a haemorrhagic element with tiny discoloured spots in the depth of the skin, those nodes never suppurated or desquamated. The nodules described in this paper contain a necrotic centre and have shown a tendency to fibrosis with sometimes slight scaling over the opaque spot, resembling more the condition we have seen clinically in acute lupus erythematosus than the Osler node. These lesions are seen both in the disseminated discoid and in the acute visceral variants. Such tender, red nodules, often with slight induration, occurred in ten out of forty-two fatal cases of generalized lupus erythematosus and in four out of seventeen patients who subsequently recovered and who probably represent dissemination of a chronic discoid lesion (Bywaters and others, 1939). The finger and toe pads in that series were tender, swollen, sometimes with haemorrhagic areas, sometimes papular or blistered, and often ending in local desquamation, just as in Case 2 above. In six out of seven cases where blood cultures were made, findings were negative, and in only one of ten cases was verrucous endocarditis (Libman-Sacks) found at necropsy. Libman and Sacks (1924), Keil (1938), Coburn and Moore (1943), Ginzler and Fox (1940), and others have also seen such digital lesions in cases of verrucous endocarditis and lupus erythematosus. No biopsy examinations on these finger lesions of lupus erythematosus are available, and the histology of the Osler node rests upon two reports only (Merklen and Wolf, 1928; Lian and others, 1929), and our own observations (Glynn and Bywaters, unpublished data). It is enough to say that these lesions are not in the least like those figured in this paper, being merely what one might expect from a mildly septic embolus. In cases of primary or para-amyloidosis simulating scleroderma (Gottron, 1932), dermatomyositis (*Acta path. mic. scand.*, 1944), lupus erythematosus (Brunsting and Macdonald, 1947), and rheumatoid arthritis (Magnus-Levy, 1938), small digital nodules are sometimes seen, occasionally with painful finger tips (Michelson and Lynch, 1934). These turn out histologically, however, to be amyloid infiltrations of vessel walls (Weber and others, 1937). Finally, it is necessary to distinguish between nodules arising in the true skin and those arising in subcutaneous tissues which ulcerate through the skin to the surface, a phenomenon we have studied histologically in two cases.

Palmar and Digital Contractures.—These lesions, seen in Cases 1, 2, and 3, seemed to resemble Dupuytren's contracture, with flexion at the proximal interphalangeal and metacarpo-phalangeal joints: they involved the palmar fascia, which was adherent to the skin, producing dimpling on extension of the fingers. In Case 2 this was associated with a palpable swelling in the palm. A striking factor was the involvement first of one hand and then, a day or so later, of the symmetrical fingers of the other hand while the first had become free again. The probable mechanism is a rapidly evolving granuloma of the palmar aponeurosis. While we have seen, not infrequently, in rheumatoid and gouty cases, nodules in the tendons and in the tendon sheaths, these have produced, not acute transient finger contractures, but finger fixation or pseudo-ankylosis. Only very briefly in the development stage of such chronic granulomata does the patient complain of the finger momentarily sticking. Similar contractures have been seen by Scheele (1885) in a boy of 13 years with chorea and nodules involving the third, fourth, and fifth fingers of both hands lasting less than one month. Keil (1938) records a case of rheumatic fever in a girl with profuse nodule formation who developed bilateral third and fourth finger contractures of Dupuytren type with nodules in the palmaris longus fascia. Berkowitz (1912) records three cases of rheumatic fever in children, with many nodules showing similar transient finger contractures lasting

between one week (Case 1) and one month (Case 2), and we have recently seen a similar transient contracture due to palmar nodule formation in three children with rheumatic fever. Flexion contractures of the fingers have also been seen in a case thought clinically to be lupus erythematosus, but found at necropsy to have periarteritis (Bywaters and others, 1939). We have found no reference to such transient contractures in rheumatoid arthritis.

Relation to Lupus Erythematosus.—Synovitis is one of the characteristic manifestations of lupus erythematosus. It is usually mild: the biochemical and cytological changes in the synovial fluid differentiate it from rheumatoid arthritis, and the synovial membrane histologically appears different (Bywaters, Doniach, and Nellen, 1947). But occasionally lupus erythematosus patients are seen with joint deformities clinically and radiologically indistinguishable from rheumatoid arthritis: in eight of forty-two patients, deformity or spindling was present (Bywaters and others, 1939), and in one recent patient excised subcutaneous nodules closely resembled the rheumatoid granuloma. The clinical resemblance of the finger-tip lesions of the cases described in this paper to those of acute lupus erythematosus, the presence of pericarditis in Case 2, and finger contracture in lupus erythematosus has already been noticed.

It will have been remarked also that Case 2 showed a butterfly erythema of the face with slight residual squaming and widening of the pores, clearing up rapidly but leaving telangiectasia over the nose. Thus in her case there were grounds for supposing that she had acute lupus erythematosus. Arthritis, serositis, albuminuria, fever, facial rash, finger-tip lesions, and leukopenia, which are the most important features of acute lupus erythematosus, were all seen in this patient. Despite this, there are two points against that hypothesis. Thus in acute lupus erythematosus with albuminuria, recovery is very rare and it is unusual for a remission to last as long as this has done. Secondly, I have neither seen a case nor found records of cases with multiple large nodules, although, as mentioned above, a recent and unique case of typical discoid lupus erythematosus, with dissemination and visceral involvement ultimately recovering, has shown two nodules closely resembling those of rheumatoid arthritis. While Case 2 could be made to fit either pigeon-hole, she fits better into this series of rheumatoid arthritis (variant form with cutaneous nodules). The other patients showed no multiplicity of signs relating them to lupus erythematosus.

Relation to Lipoidosis.—While Layani (1939) and Weber (1944) have each published a case of joint disease apparently resembling rheumatoid arthritis with xanthomatous nodules associated with raised cholesterol figures (maxima 1,344 and 350 mg. per cent. respectively), only one case has been described (by Graham and Stansfield, 1946), where a rheumatoid-like type of joint deformity due to xanthomatosis has been associated with a normal blood cholesterol. Histologically there was no evidence at all of any rheumatoid-like process. Radiographs of the hands (which Dr. George Graham kindly allowed me to see) showed erosions of subchondral bone closely resembling that seen in rheumatoid arthritis but with several abnormal features such as para-articular erosions and rarefactions which are not seen in rheumatoid arthritis, substantiating the view that this was primarily a granulomatous infiltration of tendon and capsular insertions by xanthoma cells. The character of the joint lesions and nodules left no doubt that this was a primary xanthomatosis mimicking rheumatoid arthritis in the same way that amyloid infiltration of the joints sometimes does in multiple myelomatosis (Stewart and Weber, 1938). In Layani's case (detailed fully by Vishnevsky, 1939) the radiographs of the hands are (contrary to her statement, "ce ne sont pas les mains de rheumatisante") typical of an advanced stage of rheumatoid arthritis, and we have seen several such "mains-en-lorgnette" with quite normal cholesterol levels. It seems probable that that case was one of hypercholesterolaemia complicating an established rheumatoid arthritis with quite typical radiographs at four years from onset and three years before the first blood analysis.

A remarkable clinical story resembling in several respects that of Case 1 is recounted by Reed and Sosman (1942).

A Jewish woman, aged 21, complained of recurring migratory attacks, over a year or so, of pain, swelling, heat, and limitation, lasting in each joint for one or two days and affecting hands, wrists, elbows, hips, knees, and feet. The adjacent soft tissues would also on occasion become swollen. In between attacks these joints were quite normal. Active use of the joints and cold both tended to produce symptoms, the picture of which was not unlike rheumatic fever. Small subcutaneous nodules on the posterior aspect of both arms appeared, lasting several days and leaving ecchymotic spots. She suffered from sore throats, epistaxis, and loss of weight. Moderate enlargement of the metacarpo-phalangeal joints of both hands was seen, with soft-tissue swelling over the dorsum and spindling of the digits: however, there was neither heat, pain, nor limitation of movement. There was a rough systolic murmur in the basal area; A-V conduction was prolonged. The erythrocyte sedimentation rate was 15 to 18 mm. in one hour, the cholesterol 149 mg. per cent., leucocytes

5-6,000 per c.mm. of blood. Thus so far the story is very similar: but the patient had typical attacks of "osteomyelitis" with drainage in both femora at the age of 10 and 13, and biopsy of the bones showed typical Gaucher cells. Radiographs showed enlargement of spleen and liver, many irregular cystic defects in the long bones, and flask-shaped femora. The hands showed narrowing of interphalangeal joints without erosion. In our own patient Gaucher's disease is ruled out on histological, clinical, and radiological grounds, and indeed the above history is unique and not at all characteristic of the usual case of Gaucher's disease.

In Case 1 some of the radiological changes, especially those developing in the terminal phalanx of the left big toe, resembled lipoid infiltration as seen for instance in the Hand-Schüller-Christian syndrome. Bone biopsy (of the finger) showed, however, neither the characteristic picture of this nor of Gaucher's disease. The marrow spaces were filled by small, regular, somewhat finely vacuolated cells which might have been filled with lipoid (no fat stain was done) as is sometimes seen in other granulomata, for example, in rheumatoid nodules and in the pigmented villous xanthogranuloma with giant cells and iron filled macrophages occurring in the joint cavities or tendon spaces (Jaffe and others, 1941) and thought now to be a sclerosing haemangioma with retention of macrophagic properties for iron granules or fat. Indeed, a modern view of Hand-Schüller-Christian's syndrome is that this condition is not a primary disturbance of lipoid metabolism but a chronic granuloma, with secondary lipoid characters closely related to Letterer-Sive disease, eosinophilic granuloma of bone, and osteitis fibrosa disseminata (Albright), and possibly related to the reticuloses (see Mallory, 1942). Certainly the presence of cholesterol is very common in rheumatoid nodules, both as crystals in the central necrotic area and in the cells forming the palisade layer, presenting in haemotoxylin-and-eosin-stained sections as foam cells. I have also seen large crystals of cholesterol floating free in synovial fluid from such cases. There seems to be no reason for separating such cases from the ordinary type of rheumatoid arthritis with nodules showing only a small amount of cholesterol, as Fletcher (1946) has done. This has already been recognized by Kersley and others (1946), who stress also the presence of cholesterol in gouty nodules (see also Chauffard and Troisier, 1921).

Thus, despite the atypical radiological appearances, we do not believe that this case falls into the category of lipoidosis, either primary, secondary, or granulomatous. Biopsies from other places showed no evidence in favour of this hypothesis, and indeed even the radiological appearances differ very considerably from that of the hands in the only published case of xanthomatosis with joint involvement and normal cholesterol (Graham, personal communication).

Relation to Palindromic Rheumatism.—"Palindromic" (recurrent) rheumatism was described as a new syndrome by Hench in 1940. The full description by Hench and Rosenberg (1944) of thirty-four cases has been largely confirmed by subsequent case reports. It seems to be comparatively rare, since Hench's estimate of five or six cases per year is from a total annual turnover of 4,000-4,500 new cases which are already highly selected. It is characterized by recurrent transient attacks of joint pains and swelling which last a few hours or days and then subside completely, but, unlike intermittent hydrarthrosis, very many joints are affected in turn. Attacks may occur daily, usually towards evening, or more often, or several times a year only, lasting over a period of many years, for example, up to twenty-five years, without leaving any clinical, histological, or radiological residua. In an attack the synovial membrane is inflamed and the joint contains a fibrinous polymorphonuclear exudate. Para-articular soft-tissue swellings also occur, affecting the dorsum of the hand or the upper forearm or elsewhere. Intracutaneous and subcutaneous nodules were found in three cases, in the digital pads or over the fingers, occurring at sites of pressure: one such nodule was biopsied but no central necrosis or palisade was seen. Tenosynovitis with effusion and hoarseness of the voice was also noticed. The sedimentation rate was raised (average 32 mm. in one hour in sixteen cases during or just after an attack); blood uric acid was normal; cholesterol was slightly raised (between 225 and 315 mg. per cent. in nine of eleven patients), and slight leucocytosis was present in some cases but in no case was this higher than 16,800 per c.mm. of blood. In two patients slightly subnormal figures were found.

This general picture is confirmed on the clinical side by ten out of thirteen subsequent publications under this title reporting twelve cases (Cain, 1944; Thompson, 1942; Mazer, 1942; Ferry, 1943; Paul and Logan, 1944; Grego and Harkins, 1944; Paul and Carr, 1945; Wingfield, 1945; Neligan, 1946; Hopkins and Richmond, 1947). Five cases recorded under this title by Saloman, 1946, and Perl, 1947, have not been included as confirmatory since the data given are insufficient to make a diagnosis. Of the two cases briefly recorded by Weber (1946), the first suffered from recurrent pain in the hip joints, migraine, and iritis but showed no real

similarity to palindromic rheumatism as defined by the originator of the term. (The second case cited by Weber is Case 1 of this paper, and was thought to be "half way between palindromic rheumatism and angioneurotic oedema"). It will be seen, therefore, that the diagnosis of palindromic rheumatism fitted Case 1 very well until it was discovered firstly that radiological changes were present, secondly, that the nodules were of rheumatoid type with central necrosis, and thirdly that cartilage destruction was occurring, as evinced by the finding of cartilage detritus embedded in and undergoing absorption by synovial membrane.

Case 2 also showed many of these features; articular swellings related to housework, cutaneous nodules related to pressure, hoarseness, teno-synovitis, and para-articular swellings in the palm, on the dorsum of the hand, and in the forearm, closely corresponding to Hench's description. But she had well-marked radiological changes of rheumatoid arthritis, and like Case 1 the nodules, cutaneous and subcutaneous, were those of rheumatoid arthritis.

Case 3 was even more clearly one of rheumatoid arthritis, but again she presented the digital pad lesions and the palmar contractures shown by the other two cases. Hench and Rosenberg (1944) have concluded on the basis of their experience that this picture is *not* merely a palindromic variant of rheumatoid arthritis. On the basis of our much smaller experience we would conclude that the cases we have described form a "palindromic" variant of rheumatoid arthritis: this is based on the presence of rheumatoid nodules and radiological bone changes. While it is possible that the one nodule that Hench biopsied was atypical, or that the section failed to include the central necrotic area, it is more likely that his description is correct and that these nodules of palindromic rheumatism are entirely different from those of rheumatoid arthritis. It is even more difficult, if we are describing the same syndrome, to account for the complete absence of significant radiological bone change in Hench's thirty-four cases and the ten cases described by other authors, and its presence in our case. The possibility exists, of course, that radiological change will occur given a long enough follow-up, as indeed happened in Case 1. When seen by Dr. Parkes Weber in 1942 (Weber, 1946) no radiological changes were visible, but five months later such changes were quite obvious in both hands and feet. It is difficult to think, however, that this possibility applies to most of the recorded cases whose disease had lasted, before radiographic examination, for many years (average of seven years for Hench's thirty-four cases). We must conclude, therefore, that the syndrome we are describing is not palindromic rheumatism, but a rheumatoid variant which may approach it very closely, all degrees of which, from the fairly straightforward rheumatoid of Case 4 to the highly "palindromic" degree of Case 1, may be manifest. It would be interesting to know whether such cases as ours occur in the vast material presenting annually at the Mayo Clinic. This conclusion of ours is in agreement with the views of Walter Bauer and his group at the Massachusetts General Hospital. Thus, Ropes (1944) states that "of the relatively few typical cases of this (i.e. palindromic) syndrome seen in our clinic, the majority have occurred in patients with definite evidence of rheumatoid arthritis . . . *x*-ray changes or progressive symmetrical joint disease". She points out further that intermittent hydrarthrosis also, in the majority of their cases, is a phase in the development of rheumatoid arthritis, a view supported by the observations of Ghormley and Cameron, 1941, and Cecil, 1940. Kuhns (1945) also remarks that he has seen three cases diagnosed as palindromic rheumatism who later developed damage to the articular surfaces and pronounced deformities. Given a long enough follow up, will all cases show this?

It should be added finally that there is nothing to suggest that these cases fall into the rather obscure and doubtfully distinct categories of angio-neural arthrosis (Solis-Cohen) or allergic arthritis (Kahlmeter).

Relation to Gout.—There is no evidence that any of these cases suffered from gout. At the same time, the recurrent attacks of arthritis in gout, with complete restitution in the early phases and gradually progressive permanent involvement in the later stages, and the appearance of nodules or tophi which histologically closely resemble rheumatoid nodules except for the uric acid crystals and their accompanying giant cells, all point to a somewhat similar pathological process in that disease. This has been previously pointed out by Verhoeff and King (1938) in their discussion of rheumatoid scleromalacia perforans. That joint involvement can occur as the result of a metabolic disease is seen not only in gout, and in Graham's case of "lipoid gout" cited above, but in para-amyloidosis with or without multiple myelomatosis, where subcutaneous ulnar nodules may also be found (Tarr and Ferris, 1939). Case 1 was, in fact, thought for a long time to be and was treated as, one of gout. The value of "Atophan" was perhaps doubtful, as it is in gout, but it was the only drug that the patient continued to use fairly

consistently. The case illustrates even better than classical rheumatoid cases these clinical and pathological similarities with gouty arthritis. While, viewed from the standpoint of a biochemist, every disease may be considered as a metabolic disease, we submit that there is a very special case for considering rheumatoid arthritis (and specially such a variant as we have described) from this point of view. The metabolic view of gout has led us only a little nearer to an understanding of its genesis, but recent studies on biochemical changes in unaffected relations of gouty patients (Talbott, 1940) and on the heredity factor in rheumatic fever (Wilson, 1940) point to relatively unexplored avenues of approach in the rheumatic diseases.

Relation to Rheumatoid Arthritis.—This series of cases shows a graded passage from Cases 4, 5, and 6, a not very unusual type of rheumatoid arthritis, to Case 3 (with the characteristic transient palmar contractures and digital pad nodules), to Case 2 (still showing characteristic rheumatoid radiological findings), to Case 1 (in whom the differences from accepted ideas of rheumatoid arthritis were so great that nine eminent specialists were unable to make that diagnosis). Yet these four cases obviously resemble each other far more than, for instance, Case 1 resembles palindromic rheumatism or Case 2 lupus erythematosus. Histological criteria establish them all as rheumatoid arthritis, and, in the absence of direct aetiological identification (as by the finding of a specific organism), the only definitive criteria of a disease entity are such anatomical specificities and such a common (although uncommon) clinical picture.

We believe that this is a variant of a pathological process which, under other slightly different circumstances, produces classical rheumatoid arthritis, and which is related again but more distantly to others of the unexplained mesenchymal disease, such as palindromic rheumatism, lupus erythematosus, scleroderma, dermatomyositis, peri-arteritis nodosa, and possibly even gout. While for the purposes of diagnosis and hence for prognosis and treatment differences between syndromes are to be emphasized, for non-utilitarian or research purposes it is the similarities in each different syndrome which should be explored. Pigeon-holing of sick men and women is a necessity to the clinician in his daily craft but a hindrance in his pursuit of truth. Emphasis of that point is the purpose of this presentation.

Summary

Three cases are described in detail of a variant type of rheumatoid arthritis with transient digital pad nodules, transient palmar contractures, and transient para-articular swellings. Biopsy material showed the nodules to be of rheumatoid type. Radiologically, changes in the juxta-articular bone were seen, atypical in Case 1 and identical with those of rheumatoid arthritis in the others. Case 2 showed pericarditis, leukopenia, fever, albuminuria, a butterfly rash, and other features often seen in acute disseminated lupus erythematosus with visceral manifestations. The relation of these cases to palindromic rheumatism and to other mesenchymal diseases is discussed.

I would express my gratitude to my colleagues at the Postgraduate Medical School of London for their assistance and co-operation. I am indebted also to Victor Willmott for the photographs and to Messrs. Baker and Griffin who prepared the sections.

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Une forme d'Arthrite Rhumatismale Caractérisée par la Récurrence de Nodules de la Pulpe Digitale et de l'Atteinte de l'Aponévrose Palmaire, Analogue au Rhumatisme Palindromique

RÉSUMÉ

L'auteur décrit en détails trois cas d'une variété d'arthrite rhumatismale avec apparition transitoire de nodules de la pulpe digitale, de contractures palmaires, et de gonflement para-articulaire. La biopsie a montré que ces nodules étaient du type rhumatoïde. A l'examen radiologique on a constaté des modifications des os voisins de l'articulation, modifications atypiques chez le sujet 1 et identiques à celles de l'arthrite rhumatismale chez les autres. Le sujet 2 présentait de la péricardite, de la leucopénie, de la fièvre, de l'albuminurie, une éruption en papillon, et d'autres manifestations fréquemment présentes dans le lupus érythémateux disséminé aigu avec des manifestations viscérales. L'auteur discute la relation entre ces observations et le rhumatisme palindromique et d'autres affections du tissu conjonctif.

THE METABOLISM OF HYALURONIC ACID IN RELATION TO RHEUMATIC DISEASES*

BY

HENRY COHEN

The diffidence with which I approach the subject of hyaluronic acid and rheumatism is born of a conjugation of both personal and general ignorance. Our knowledge of the functional and intrinsic pathology of that group of locomotor disorders which we label "the rheumatic diseases" is so meagre that any new facts, however tenuous their nexus with rheumatism may appear to be, are seized on avidly and too often uncritically in the hope, as yet practically unrealized, that they will throw some light on the mechanisms of the "rheumatic" process. How comes it to be thought that a knowledge of hyaluronic acid and the enzyme, hyaluronidase, might help in the interpretation of the phenomena of rheumatic diseases?

I have argued previously that there is no common specific aetiology for the whole group of rheumatic disorders, but that they have two common features, namely, the site of attack and the structural changes they exhibit.

The site of the rheumatic lesion is in the skeletal tissues of mesenchymal origin, viz. connective tissue, fascia, muscle, ligament, joint capsule, synovial membrane, articular cartilage, and even bone. These all contain collagen.

The basic pathological lesions of rheumatism are, however, to be found not only in these tissues but also in the blood vessels which supply them. The basic lesion was described by Klinge as a fibrinoid degeneration or swelling of the collagen bundles of mature fibrous tissue. The earliest change is that of swelling of the fibres, which later show granular degeneration and fragmentation, and at the same time oedema occurs in the interstitial spaces. This leads to a partially necrotic area with fragmentation of surviving collagen fibres. There occurs also degeneration of the inter-fibrillar ground substance or cement. These foci act as irritants to the tissues, giving rise to inflammatory changes of a granulomatous type which may resolve by fibrosis. The vascular change has been described by Collins and others. It is essentially an arteritis involving all coats of the vessel and may lead to thrombosis.

I have mentioned that connective tissue consists essentially of collagen fibrils and of the inter-fibrillar ground substance or cement. Chemical studies have shown that amongst the constituents of this ground substance are chondroitin sulphuric acid and hyaluronic acid, and that both of these can be acted upon by the enzyme, hyaluronidase.

Isolation of Hyaluronic Acid

Hyaluronic acid was first isolated from bovine vitreous humour, and later studies have revealed its presence in other mucoid tissues, such as synovial fluid, connective and subcutaneous tissue, A and C haemolytic streptococci in the mucoid phase, and the capsule of the ovum. It is a simple viscous mucopolysaccharide, made up of equimolecular amounts of N-acetylglucosamine and glucuronic acid. A detailed review covering its occurrence, chemistry, isolation, methods of estimation, the mechanism of the action of hyaluronidase on hyaluronic acid, the influence of such environmental factors as *p*H and salts, and of inhibitors such as heparin, chondroitin sulphate, gastric mucin and abnormal serum, is to be found in an article by Karl Meyer in *Physiological Reviews*. For our purpose it should be recalled that hyaluronic acid forms gels with proteins but is not antigenic.

The highest concentration of hyaluronic acid is found in mammals in the synovial fluid (0·02 to 0·05 per cent. in the normal but up to five times this quantity in the abnormal), and it is responsible for 80 to 90 per cent. of the viscosity of the fluid. That hyaluronic acid is a specific secretion of synovial cells is suggested by two facts: first, if synovial tissues be cultured they produce hyaluronic acid; and, secondly, that metastases from synoviomata also produce it.

Hyaluronidase

The enzyme, hyaluronidase, breaks down hyaluronic acid apparently in two stages; first there is a rapid diminution in viscosity due, it is suggested,

* This was the opening paper of a discussion on hyaluronic acid in rheumatic diseases at a meeting of the Heberden Society on Oct. 16, 1948.

to depolymerization of the acid and, secondly, to its breaking up into its constituents—N-acetyl-glucosamine and glucuronic acid. Hyaluronidase has an interesting history. In 1931 McLean showed that certain organisms produced a substance which markedly increased the area of spread of a dye injected into the subcutaneous tissues. This he called the *spreading* or *diffusing* factor. My interest in this factor arose from studies on the choroid plexus and ciliary body which revealed that their cells elaborate a spreading factor which plays a part in the diffusion of cerebrospinal and intra-ocular fluids. In 1939 Chain and Duthie showed that the activity of the spreading factor ran parallel with the hyaluronidase content of the extract, and it was later demonstrated that the spreading factor was almost certainly identical with hyaluronidase.

This enzyme is of wide distribution. It is found not only in such organisms as rough (Type II) pneumococci, A and C haemolytic streptococci, staphylococci, and many anaerobes, but also in leeches, snake venom, and especially in the testis, from which most preparations of hyaluronidase for experimental purposes have been made. There is considerable evidence that it is the hyaluronidase of the spermatozoon which enables the fertilization of the ovum to occur. The capsule of the ovum, as we have earlier noted, contains a considerable amount of hyaluronic acid, and is surrounded by granulosa cells clumped together by this acid; fertilization will occur only when the enzyme has so disrupted the acid that the sperm can enter. Almost certainly several hyaluronidases exist with differing actions on the mucopolysaccharides, and evidence of their specificity has been obtained by antigenic reactions.

It is then clear that when hyaluronidase acts on the mucopolysaccharides of connective tissue there may result (i) oedema of both tissue fibres and spaces, (ii) a fragmentation of collagen fibres and the intercellular cement, and (iii) a reduced viscosity of synovial fluid. This last is of considerable interest. The normal synovial fluid on dilution, acidification, and the addition of normal horse serum gives rise to a fibrinous clot, but pathological fluids subjected to similar treatment give simply a colloidal turbidity. If, however, a small amount of hyaluronidase (0·01 unit, which is insufficient to affect either viscosity or hyaluronic acid concentration) be added to a normal fluid and treated similarly, a colloidal turbidity similar to that found in pathological fluids occurs, suggesting the presence of an excess of hyaluronidase in the pathological fluid. This has been expressed quantitatively by the following formula:

Where V = viscosity of fluid and C_H = concentration of hyaluronic acid determined turbidometrically, then $\frac{\log V}{C_H}$ exceeds 10 for normal fluids, and is less than 10 for pathological fluids, the activity of the disease being, roughly, inversely proportional to this factor.

Thus it appears that when the enzyme hyaluronidase attacks hyaluronic acid and other ground substances of connective tissue there occurs a series of changes analogous to those seen in rheumatic diseases. But we must not fall victims to that most elementary of logical fallacies—the middle term—and assume that the same effect necessarily results from identical causes.

There are, however, a few published observations which suggest that studies of hyaluronic acid metabolism may yield useful information for our studies of rheumatic disease. First, Guerra has suggested that the beneficial effects of salicylates in rheumatism result from the antagonism of this drug and hyaluronidase which he and others claim to have demonstrated; their results have not always been confirmed, but it may well be that different forms of hyaluronidase have been used in the different experiments. Secondly, normal serum inhibits hyaluronidase in a non-specific manner, but this inhibitory power is said to be increased in rheumatic disorders possibly as a result of antigenic activity of hyaluronidase accompanying the disorder; there is, however, no clear indication that this is of great significance in "rheumatism". Thirdly, hyaluronic acid after intravenous injection prolongs the erythrocyte sedimentation rate *in vitro*, and it has been shown that purified testicular hyaluronidase decreases *in vitro* the E.S.R. of those suffering from rheumatic fever, but this is most likely to be due to spherocyte formation and not to direct antagonism of hyaluronidase and hyaluronic acid. And, fourthly, we may recall that certain organisms produce hyaluronidase and in this group are haemolytic streptococci which have commonly been regarded as playing a part in the genesis of rheumatic disorders, but the evidence is conflicting and with many organisms no correlation has been shown between hyaluronidase production and their virulence, or association with rheumatic disease.

The Present Position

This brief survey is but the background of a vast problem. It cannot be claimed that as a result of the knowledge thus far attained we stand on the brink of a new era in our understanding of rheumatic disease. Indeed we cannot as yet assert that any direct association between hyaluronic acid metabolism and rheumatism has been established. The

evidence is, however, suggestive and a fruitful field of study has been revealed which merits further exploration. The history of rheumatism is itself the most forceful warning against the uncritical acceptance of hypotheses however intriguing, alluring, or seductive they might appear. We may mourn the slaughter of a beautiful hypothesis by an uncompromising fact, but the tragedy must unresentfully be accepted.

The most gratifying features of these researches on hyaluronic acid and hyaluronidase are, first, that they reveal the wider recognition of the fact that we must have a deeper understanding of the fundamental problems of connective tissue metabolism if we are to have a clearer knowledge of " rheumatism ", and, secondly, that they indicate that we are receding from an era in which the literature of rheumatic disease concerned itself, often exclusively, with the miraculous changes wrought by a specific elixir.

Le Métabolisme de l'Acide Hyaluronique et ses Rapports avec les Affections Rhumatismales

RÉSUMÉ

Lorsque l'acide hyaluronique et d'autres substances fondamentales du tissu conjonctif sont attaquées par l'enzyme hyaluronidase, il semble qu'il se produise une série de modifications analogues à celles que l'on observe dans les affections rhumatismales. Mais, remarque l'auteur, il ne faut pas succomber au sophisme qui consiste à conclure que les mêmes effets sont inévitablement produits par les mêmes causes.

Néanmoins, certaines observations publiées suggèrent que l'étude du métabolisme de l'acide hyaluronique pourrait fournir des renseignements utiles pour l'étude des affections rhumatismales. Premièrement, Guerra a suggéré que l'action favorable des salicylates dans le rhumatisme serait due à l'action inhibitrice de ce médicament sur l'hyaluronidase, que lui et ses collaborateurs croient avoir démontrée; leurs résultats n'ont pas toujours été confirmés, mais cela peut être dû à ce que l'on n'a pas toujours utilisé les mêmes formes d'hyaluronidase dans les différentes expériences. Deuxièmement, le sérum normal inhibe l'hyaluronidase de façon non spécifique, mais ce pouvoir inhibiteur serait accru dans les affections rhumatismales peut-être par suite de l'activité antigénique de l'hyaluronidase présente au cours de cette maladie; il n'y a cependant aucune indication précise que ceci ait une grande importance dans le " rhumatisme ". Troisièmement, l'acide hyaluronique injecté par voie intraveineuse abaisse la vitesse de sédimentation des globules rouges *in vitro*, et il a été prouvé que l'hyaluronidase testiculaire purifiée diminue *in vitro* la vitesse de sédimentation des globules rouges des malades atteints de rhumatisme articulaire aigu, mais ceci est très probablement dû à la formation de sphérocytes et non pas à l'antagonisme direct entre l'hyaluronidase et l'acide hyaluronique. Et, quatrièmement, on se souvient que certains micro-organismes produisent de l'hyaluronidase, dans ce groupe se trouvent les streptocoques hémolytiques qui ont été couramment considérés comme jouant un rôle dans la génèse des affections rhumatismales, mais les faits se contredisent et, dans le cas de nombreux micro-organismes, on n'a pu démontrer aucune corrélation entre leur production d'hyaluronidase et leur virulence, ni leur association avec les affections rhumatismales.

Ces recherches sur l'acide hyaluronique et l'hyaluronidase sont surtout intéressantes, premièrement, parce qu'elles montrent que l'on admet de plus en plus la nécessité d'arriver à une compréhension plus complète des problèmes fondamentaux du métabolisme du tissu conjonctif pour clarifier nos connaissances sur le " rhumatisme ", et, deuxièmement, parce qu'elles indiquent que nous dépassons la période pendant laquelle la littérature sur les affections rhumatismales ne s'intéressait, souvent exclusivement, qu'aux changements miraculeux produits par un élixir spécifique.

SYNOVIAL FLUID MUCIN*

BY

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Synovial mucin, the characteristic component of synovial fluid, was first isolated in 1846 by Frerichs (1846), who precipitated it from joint fluid by addition of acetic acid. Its high viscosity and peculiar chemical composition made it a subject of much interest. Frerichs realized that it was a complex of protein and carbohydrate components, but little additional information was added until the 1930's, when hyaluronic acid, the carbohydrate component, was isolated and more closely studied. Even so, much confusion still exists concerning both the constitution of hyaluronic acid and the type of linkage by which it can unite with protein. The question is still unsettled whether connective tissue mucins found in different situations in the body are all similar or whether there are a great variety of mucins differing one from another in the character of their protein groups or even also in the hyaluronic acids they contain.

With regard to the physiological role of the mucins, we have hardly got beyond the realm of speculation, and their actual relation to disease processes is therefore equally obscure.

Within recent years several different lines of approach have been made towards these various problems, particularly as regards the synovial mucin of joints, and it is my intention to describe to you briefly what progress has been made towards an understanding of the chemical and physiological fields.

Distribution of Mucins

The mucins are very widely distributed in the animal kingdom and throughout the different parts of the human body. They are acido-glycoproteins, that is to say, complexes of protein united to a polysaccharide which possesses acidic characteristics, but a subdivision is possible according to whether the carbohydrate is rendered acid by virtue of sulphuric acid groups—as in the chondroitin sulphuric acid of cartilage—or of uronic acid units as in synovial mucin and vitreous humour. In either case they appear to act as cementing substances or extra-cellular ground substance in the connective tissues.

Most tissues of mesenchymal origin appear to produce the uronic acid type of mucin, collectively termed hyaluronate or hyaluronic acid mucin, and as examples may be cited synovial fluid, umbilical cord, lung, malignant tumours of the pleura, aqueous and vitreous humours, connective tissue generally, and skin connective tissue. It is also produced in abnormal quantities in myxoedema (Ord, 1878, Halliburton, 1888; Ropes and others, 1947; Martin and Hynes, 1948).

Either the acid polysaccharide, hyaluronic acid, or mucin can be isolated from these sources, and it is often difficult to say whether in the tissues the polysaccharide is free or actually bound to protein. In the case of synovial fluid the evidence is conflicting, but since the synovial cavity can be rightly regarded as a tissue space, it is not surprising to find within it a mesenchymal type of mucin. Destruction of hyaluronic acid by the enzyme hyaluronidase or other " spreading factors " loosens the intracellular cement and permits an abnormal diffusion of substances into and from the tissues (Duran-Reynals, 1942).

Mucins of epithelial origin differ from the hyaluronic acid mucins in their chemical composition and reaction to enzymes. Very frequently they contain, not sugar acids, but sulphuric acid in ester linkage which confers upon them the property of staining metachromatically.

Properties of Hyaluronic Acid and of Mucins

I do not propose to deal further with the sulphuric-acid-containing mucins or chondroitin sulphuric acids, but to turn now to a more detailed consideration of hyaluronic acid itself.

This substance was first isolated from vitreous humour and then from umbilical cord by Meyer and Palmer (1934, 1936) and found to be built up from units of glucuronic acid, glucosamine, and acetic acid, the whole molecule being a high polymer of this comparatively simple structure.

Solutions of hyaluronic acid were extremely viscous, and from physical measurements of diffusion coefficient, sedimentation velocity, etc., it appears that the molecule consists of long chains having a molecular weight of at least 200,000 to 500,000.

* A Lecture delivered to the Heberden Society on Oct. 16, 1948.

By taking precautions to avoid degradation of the substance during preparation, Hadidian and Pirie (1948) have obtained hyaluronic acid preparations with viscosities nearly twice as great as the highest hitherto recorded, so the true molecular weight of the native substance may well be several millions. Hyaluronic acid is very easily degraded by oxidation, by ascorbic acid, probably on account of hydrogen peroxide formed during the autoxidation of the latter (Madinaveitia and Quibell, 1941; Robertson and others, 1941; Pirie, 1942), and by serum rich in phosphatase (Robertson and others, 1940) in addition to the various enzymes termed hyaluronidases acting specifically upon it. Even slight degradation is revealed by a pronounced drop in viscosity.

Solutions of hyaluronic acid form mucins when soluble protein is added and then dilute acetic acid. The mucin separates as a tough, ropy mass leaving any excess of protein in solution; it can be redissolved, affording solutions of viscosity approximately equal to that of the original hyaluronic acid. It is the polysaccharide, therefore, that is responsible for the high viscosity of mucins. Removal of mucin by acetic acid precipitation reduces the viscosity of synovial fluid to approximately that of water (Cajori and Pemberton, 1928).

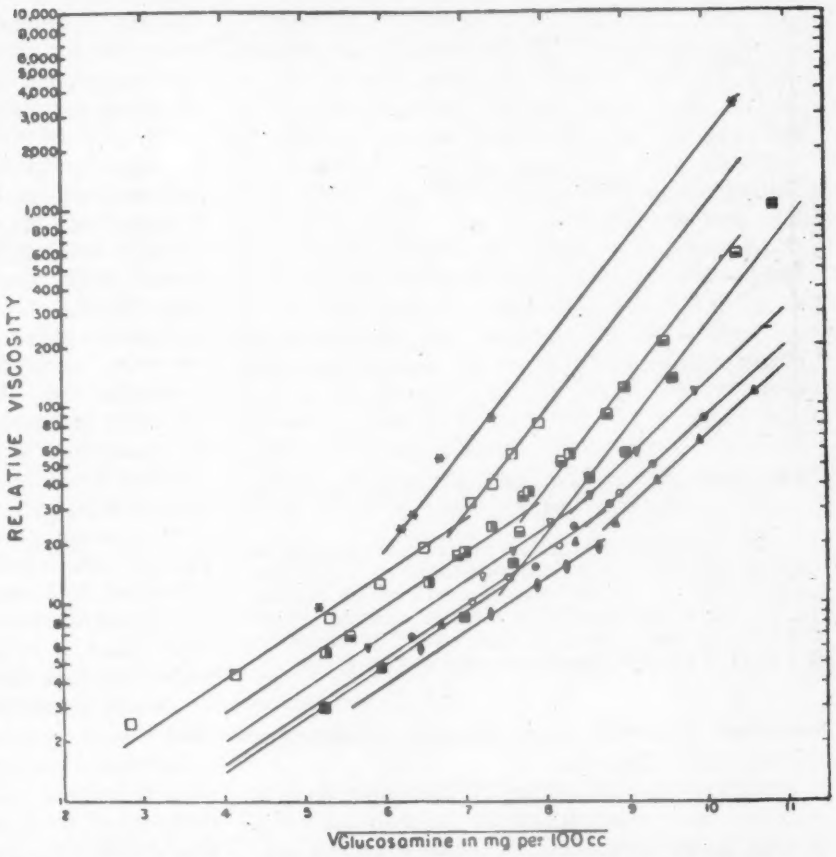

FIG. 1.—Relationship between the logarithm of the viscosity and the square root of the concentration of mucin-glucosamine in synovial fluid and in mucin and polysaccharide solutions. Viscosity measurements were made at 38° C. (After Ropes and others, 1947.) This, and Figs. 2, 3, and 5, are reproduced by kind permission of the authors and of the *Acta Medica Scandinavia*.)

Key

- * Bursal fluid (human) in 0·9 per cent. NaCl.
- □ Carpo-metacarpal and astragalo-tibial joint fluid (bovine).
- ◨ Mucin (bovine) in $\frac{M}{15}$ Na_2PHO_4.
- ▬ Mucin (bovine) in 0·5 per cent. $NaHCO_3$.
- ■ Mucin (bovine) in joint fluid (bovine).
- ▽ Mucin (bovine) in 0·5 per cent. Na_2CO_3.
- ○ Astragalo-tibial joint fluid (bovine) in 0·9 per cent. NaCl.
- ● Mucin (bovine) in serum (human) diluted with Ringer's phosphate solution.
- ▲ Mucin (bovine) in $\frac{M}{15}$ Na acetate.
- ◊ Polysaccharide (bovine) in 0·9 per cent. NaCl.

Viscosity.—The property of viscosity depends upon many factors, which will be considered in turn, such as: (1) the concentration of the solution; (2) the presence of inorganic salts; (3) the hydrogen ion concentration; (4) the temperature.

Viscosity is a manifestation of the mutual interaction between particles in solution and the relation between concentration and viscosity is not a linear one. However, a simple empirical relation has been found to hold between the logarithm of the viscosity and the square root of the mucin concentration, such plots affording a straight line; at relative

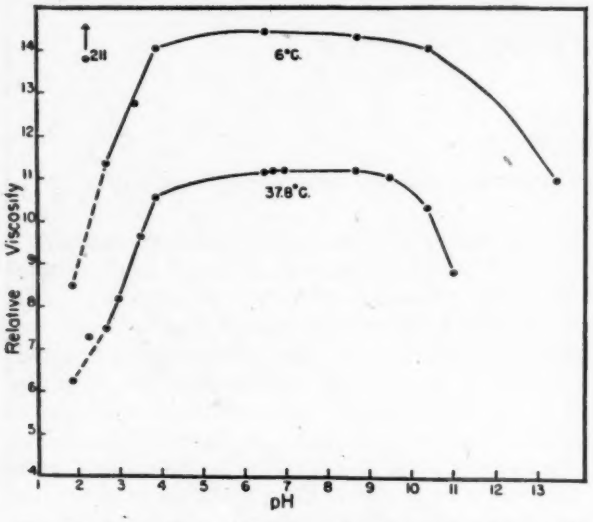

FIG. 2.—The effect of hydrogen ion concentration on the relative viscosity of polysaccharide solutions. The open circle indicates a sample which formed a gel on shaking. To 5 c.cm. of polysaccharide solution dialyzed against 0·2 N NaCl was added 0·5 c.cm. of 0·2 N NaOH or 0·2 N HCl. (After Ropes and others, 1947.)

viscosities >20 the slope changes (Ropes and others, 1947) (Fig. 1).

An interesting illustration of the dependence of viscosity upon chain length in the polysaccharide is seen in an experiment in which mucinase was allowed to act for varying periods of time upon a mucin preparation, and then a graph was made, as above, between the log viscosity and the square root of the time of action of the enzyme, the assumption being that the enzyme caused a regularly progressive diminution in mean chain length as it acted on the mucin. The result was an excellent straight line relationship, supporting the assumption. It is of interest that a similar relationship between viscosity and the chain length of molten polyesters has been found recently by Flory (1940). The experiment also indicates that we can use the viscosity/concentration relationship to compare mucins obtained from normal and diseased joint fluids. Whilst traumatic fluids have a viscosity little if anything different from normal, in rheumatoid arthritis and in specific infectious arthritis the degeneration of mucin is more marked and increases proportionally with the severity of the joint involvement (Ropes and others, 1947).

Salts.—The viscosity of mucin or hyaluronic acid solutions is markedly reduced by the presence of salts, the effect being more marked with divalent than with monovalent ions at equimolar concentration. Taking any one salt, the depression of viscosity of mucin or hyaluronic acid increases with increasing concentration of salt up to about 0·1 M. after which there is little or no increment. This effect of salts is completely reversible by dialysis.

***p*H.**—In considering the effect of *p*H upon viscosity, mucin and hyaluronic acid must be dealt with separately. Hyaluronate is little affected over a range from *p*H 10·0 to 4·0; beyond these limits viscosity falls rapidly and irreversibly (Fig. 2). In the case of mucin there is a gradual increase in viscosity from *p*H 10 to 4, at which latter point the substance precipitates. It redissolves in more acid solutions, but with a greatly diminished viscosity (Fig. 3).

Temperature.—Rise in temperature causes a reversible decrease in the viscosity of both mucin and polysaccharide solutions.

Other Properties of Mucin; Base Binding.—The isoelectric point of mucin is about *p*H 4·0 and it has a base-binding power at *p*H 7·4 of 6·4 meq./g. N. (Ropes and others, 1947). This high value is supported by calculations based on the distribution of electrolytes between serum and synovial fluid, from which it appears that synovial mucin binds about ten times the amount of calcium per gramme as do the serum proteins (McLean and Hastings, 1935).

Analytical comparison of synovial fluid with the plasma accords with the view that the former is a dialysate of blood plasma containing some protein and to which hyaluronic acid has been added by the

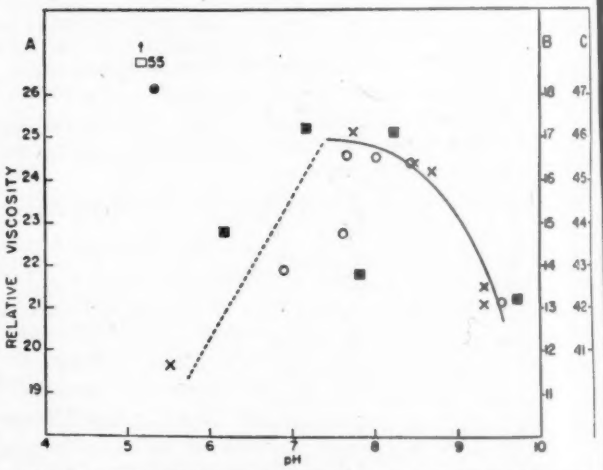

FIG. 3.—The effect of hydrogen ion concentration on the relative viscosity of normal cattle synovial fluid. Fluid A is indicated by the symbol O, fluid B by X, and fluid C by ■. The open square and the solid circle indicate samples which formed gels on shaking. To 5 c.cm. of synovial fluid was added 0·5 c.cm. of 0·2 N NaCl containing 0·2 N NaOH or 0·2 N HCl. Viscosity measurements were made at 38° C. (After Ropes and others, 1947.)

secretory activity of modified connective-tissue cells of the synovial membrane (Bauer and others, 1940).

Osmotic Properties.—Another important property of mucin is its contribution to the osmotic pressure. This has been determined indirectly by measuring the osmotic pressure of synovial fluid and comparing the figure obtained with that expected from its protein content. It transpires that the osmotic effect of mucin per gramme is nine times that of serum albumin. This is no doubt of great importance in achieving a fluid circulation through the joint in spite of the relatively low protein content of the fluid in the joint space (Ropes and others, 1939). Another illustration of the osmotic effect of mucin is seen in the swelling of the sexual skin of monkeys treated by injections of oestrogen. This causes an increase in mucin, and consequently the cells of the tissue become turgid (Ogston and others, 1939).

The State of Hyaluronic Acid in Synovial Fluid

Since both protein and hyaluronic acid are constituents of synovial fluid, it is pertinent to enquire whether they exist free or mutually associated. Acidification, as we know, leads to the precipitation of the hyaluronic acid and some of the protein as mucin, the rest of the protein remaining in the filtrate. More sensitive and discriminating methods must be used to solve the problem. Of these, electrophoresis has given what appeared to be a decisive answer. Both Hesselvik (1940) and Blix (1940) found, on subjecting synovial fluids to electrophoresis, the presence of a fast-moving component having the same glucosamine/nitrogen ratio as has hyaluronic acid, which was therefore thought to exist in the fluid free from any combination with protein.

Other physical methods such as ultra-filtration, precipitation by salts, and, in particular, viscosity

TABLE I

VOLUME OF SYNOVIAL FLUID AND MUCIN CONCENTRATION IN JOINTS OF VARIOUS SPECIES (Ropes and others, 1947)

Species	Author	Joint	Volume of fluid (c.cm.)	Mucin (g. per 100 c.cm.)
Human	Cajori and Pemberton (1928)	Knee	—	0·42[3]
	Fisher (1929)	—	—	1·95
	Achard and Piettre (1930)	Knee	—	3·0[3]
	Ropes, Rossmeisl, Peabody, and Bauer (1940)	Knee	0·13-3·5	0·85
		Knee	0·25-40·0	0·50[3]
Cattle	Frerichs (1946)			
	Newborn calves		—	0·33
	Oxen in stalls		—	0·24
	Oxen in pastures		—	0·56
	von Holst (1944)		15-20	0·5
	Fisher (1923)		—	0·13
	Ropes, Bennett, and Bauer (1939)			
	Steer	Astragalo-tibial	20-100	0·14
	Steer	Carpo-metacarpal	5-15	0·60
	Zeller, Bywaters, and Bauer (1941)			
	Calves	Astragalo-tibial	6-8	0·28
	Calves	Carpal	3·5	0·75[1]
	Davies (1944)	Hip	3-27	—
		Knee	0-42	—
		Astragalo-tibial	5-65	—
		Carpo-metacarpal	3-7	—
Horse	Bywaters (1937)	Carpal	—	0·47
	Unpublished	Astragalo-tibial	12	0·35[1]
		Carpo-metacarpal	7	0·46[1]
Rabbit	Unpublished	Knee	0·1-0·3	—
Dog	Unpublished	Knee	0·1-0·3	—
Pig	Unpublished	—	4	0·81[1]

[1] Result based on the analysis of one fluid only.
[2] Result obtained by acetone precipitation of one fluid from a patient with oedema.
[3] Fluids obtained from patients with oedema.

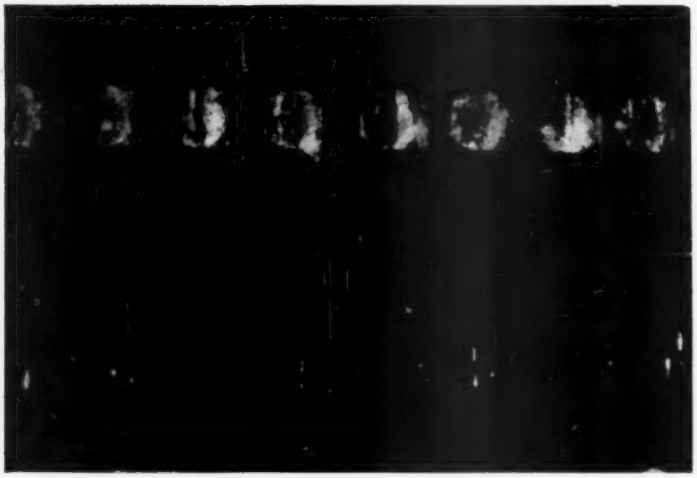

FIG. 4.—Demonstration of the "stick-slip" motion (A), and the effect of lubrication (B), the upper block of radio-active lead being caused to slide upon a lower normal block. (After Gregory, 1946, by kind permission of the author and of the Editor of *Nature*.)

studies at different *p*H, have led, however, to an exactly opposite conclusion (Ropes and others, 1947).

The viscosity of normal synovial fluid increases from *p*H 9 to 7 this behaviour being comparable with that of mucin rather than of free polysaccharide. Below *p*H 7 the viscosity falls rapidly.

It would seem that in normal synovial fluids the hyaluronic acid is probably combined with protein, although in some bursal fluids, it must be noted, hyaluronic acid alone without protein is to be found.

Physiology

The volume of synovial fluid and the concentration of mucin which it contains vary from joint to joint and also in the same joint in different animal species; but, in general, the content of mucin lies between 0·3 and 0·8 g. per 100 ml. (Table 1).

The normal human knee contains about 0·5 ml. of fluid. The astragalo-tibial joint of cattle is remarkable in containing as much as 40 ml. or more of fluid, and this source has been much used for experimental studies.

The mechanism by which mucin is catabolized is not understood, but since large molecules can only with great difficulty leave the joint cavity, it would appear that breakdown must occur in the fluid itself or in the accessory structures.

No hyaluronidase can be detected in normal synovial fluid or tissues, but both ascorbic acid and phosphatase are present and both cause degradation of mucin *in vitro* (Ropes and others, 1947).

Joint disease may affect both the formation and destruction of mucin. In traumatic lesions the volume of synovial fluid may be very greatly increased but the mucin concentration remains normal, either due to enhanced formation of mucin, or to an increase in the amount carried into the joint. At the same time the viscosity per unit concentration and the glucosamine/nitrogen ratio are so nearly normal as to indicate only slight degradation of the polysaccharide.

In rheumatoid arthritis and infectious arthritis of known origin, the joint fluid tends to be poorer in mucin, less viscous, and to give a haziness or soft mass on acidification instead of a ropy precipitate, thus indicating degradative changes in the mucin. It is noteworthy that free hexosamine can never be detected in

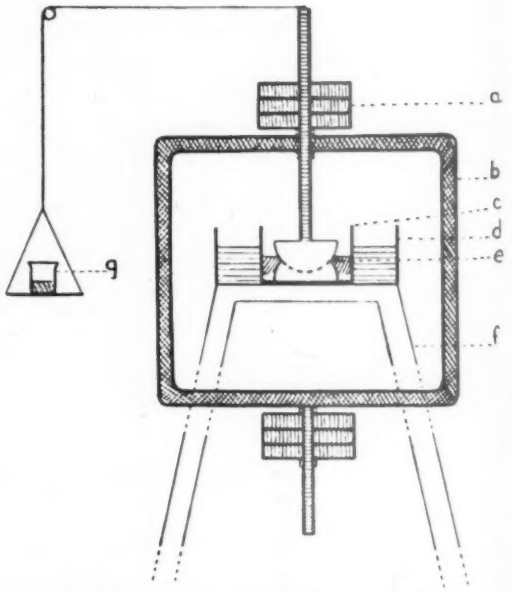

FIG. 5.—Diagrammatic presentation of the apparatus employed to study the lubricating properties of synovial fluid and mucin solutions. (a) lead weights of approximately 5 kg. each used to load the joint; (b) iron frame into which the rods carrying the weights are incorporated; (c) copper pan containing fluid to be tested—glass beads are used when necessary, to raise the level of fluid above the joint line; (d) larger copper pan containing water to regulate the temperature—the experiments were run at 38° C.; (e) articulating surfaces of lucite "joint"; (f) wooden stand supporting the entire apparatus; (g) beaker to which mercury is added in sufficient quantity to overcome friction at articulating surfaces and move joint. (After Ropes and others, 1947.)

such fluids so that the pathological breakdown is comparable only with the first stages of *in vitro* enzymatic hydrolysis.

An exceptionally high concentration of mucin is found in the synovial fluid in osteochondromatosis and also in myxoedematous patients, suggesting that the thyroid hormone plays a role in the normal regulation of mucin metabolism. The increase in mucin following administration of oestrogens has already been referred to.

Table 2, taken from Ropes and others (1947) collects some of the data relating to concentration and viscosity of synovial mucin in various types of joint disease.

TABLE 2

CHANGES IN CONCENTRATION AND STATE OF MUCIN IN VARIOUS TYPES OF JOINT DISEASE, ARRANGED IN ORDER OF INCREASING VISCOSITY (Ropes and others, 1947)

Disease	Relative Viscosity 38°	Mucin N (g. per 100 c.cm.)	Type of mucin Ppt.[2]	Nitrogen: Glucosamine
Pulmonary osteoarthropathy ..	3·2[1]	0·014[1]	P[1]	1·00[1]
Syphilitic arthritis ..	6·3	0·038	VP	1·06
Tuberculous arthritis	7·5	0·021	F	0·80
Gouty arthritis ..	12·0	0·041	F	0·94
Probable rheumatoid arthritis	12·9	0·041	F	0·82
Rheumatoid arthritis	13·1	0·067	P	1·30
Infectious arthritis ..	14·6	0·062	F	1·69
Reiter's Syndrome ..	14·9	0·074	F	1·35
Rheumatic fever ..	15·5	0·101	G	1·54
Haemophilia ..	17·4	0·048[1]	F	0·49
Lupus erythematosus disseminatus ..	25·5	0·048	G	1·37
Neuro-arthropathy ..	29·6	0·054	G	1·32
Traumatic arthritis ..	31·1	0·058	F	0·63[1]
Degenerative joint disease	45·9	0·099	F	1·04
Osteochondromatosis	137·0	0·108	G	1·41
Normal human knee joints[3]	208·0	0·066	G	1·16
Myxoedema	361·0	0·192[1]	G	—

[1] Results based on the analysis of only one fluid.
[2] The type of precipitate is expressed in symbols having the following significance: VP = few or no flecks in a cloudy solution; P = small, friable masses in a cloudy solution; F = soft mass in a clear or slightly cloudy solution; G = tight, ropey clump in a clear solution.
[3] These fluids were obtained post mortem.

Bearing on this discussion is the apparent inverse relationship between viscosity and phosphatase concentration in various joints and species (see Table 3 from Ropes and others, 1947). Phosphatase determinations in pathological joint fluids might afford some interesting data.

Lubricating Action of Synovial Mucin

The high viscosity of mucin in solution immediately suggests its possible function as a lubricating agent in the movement of the joints and the increased mucin content of joint fluid in some cases of degenerative joint disease might argue for an attempt to provide better lubrication for the damaged surfaces of the articular cartilage.

The physical phenomena of friction and lubrication are not at all simple, and I feel that it might be some help to attempt a brief analysis of these problems.

When two solid surfaces such as blocks of wood or metal are in contact it is found that a definite force is necessary to induce one to move relative to the other. This minimum force bears a linear relation to the load upon the upper block, and their ratio is known as the coefficient of static friction $\left(\frac{w}{W}\right)$. The magnitude of the coefficient of friction depends greatly upon the nature of the materials in contact, and the frictional resistance is considered to be due to an interlocking of the unevennesses forming the boundaries of the two layers in contact.

When motion takes place in the absence of any lubricant, there is jerking or tearing apart of the surfaces which is described as "clutching" or "stick-slip" motion and which rapidly leads to erosion and wear. Very beautiful pictures have been taken by Gregory (1946) of this stick-slip motion by sliding a block of radio-active lead upon a normal block and then photographing the deposit of radiant lead left upon the latter (Fig. 4).

The action of a lubricant is to separate the two sliding solid surfaces from each other by the interposition of a film or layer of liquid. A good lubricant must act so that when motion occurs the sliding which takes place is that of one liquid layer over another—in other words, a shearing effect. Our most familiar example of liquid shear is the flow of water or oil from a pipe, and it is well known that one can consider the liquid in contact with the inner surface of the pipe to be at rest while the velocity of the liquid stream increases progressively from the periphery to the centre. The rate of flow, other things being equal, depends upon the viscosity of the liquid or mutual attraction of the molecular surfaces slipping over each other.

In the case of articular surfaces bathed in a relatively deep layer of synovial fluid, we may consider the centre of the fluid to be at rest whilst the solid surfaces confining it are in motion so that the problem becomes analogous. Now in ordinary engineering practice the same set of conditions present themselves in the lubrication of a shaft and journal bearing, and a great deal of research has been applied to their investigation.

Engineers distinguish two types of lubrication, the one in which the film of oil separating the metal surfaces is extremely thin—even approaching a monomolecular layer; this is spoken of as "boundary lubrication". Such thin films acquire properties, such as abnormally high viscosity

differing from the liquid in bulk, but the conditions of boundary lubrication are not likely to occur in joints except possibly for a short time at the commencement of movement. The other case is that in which the surfaces are separated by a relatively thick layer of lubricant as normally in the joint space. Here the frictional resistance is proportional to the viscosity of the liquid and the rate of shear. The falling-sphere method of measuring viscosity makes use of this principle for, as is well known, the velocity of fall reaches a steady value related to the viscosity of the medium by Stokes's equation.

Ropes and others (1947) have designed an artificial joint for the study of the lubricating efficiency of various materials. This apparatus is shown in Fig. 5. It consists of a ball-and-socket bearing made out of the plastic substance lucite, which is weighted by lead weights on a heavy iron frame. By swinging the frame, a pendulum or circular motion may be imparted which causes the lucite surfaces to slide over each other.

With this apparatus the coefficient of static friction was measured under different loads and shown to obey the usual law. Synovial fluid was then compared with other substances such as saline or serum by introducing it between the sliding surfaces. A similar type of apparatus, but employing a human proximal interphalangeal joint, has been used by Jones (1934, 1936), and also made possible a test of the load necessary to cause a breakdown of the layer of synovial fluid separating the articular surfaces. Such a film withstood the great pressure of 900 lb. per sq. inch, more than that which is sufficient to crush bone itself.

Yet another function of the viscous layer of synovial fluid in the joint may be the provision of a damping or shock-absorbing mechanism for which a viscous material is admirably suited. The jarring and vibration associated with limb movements such as walking would thereby be taken up by the cushion of fluid and the articulating surfaces would be protected from damage. It is quite certain that cartilage, once injured, shows little or no tendency to regenerate and when repair takes place it does so by the invasion of fibrous tissue through marginal or subchondral proliferation.

When we consider the pathological changes in an arthritic joint, it may well be wondered whether lowering of the viscosity of the synovial mucin due to chemical degradation of the hyaluronic acid precedes any structural damage to the articulating surfaces or whether such damage caused by an infective or other type of agent so alters the permeability of the joint tissues that substances enter the cavity which may prove deleterious to the chemical integrity of the mucin. I am thinking, for example, here, of the possible role of phosphatase or the enzyme accompanying phosphatase which attacks mucin. Only further experiment and investigation will place these occurrences in their right relationship.

Concluding Remarks

It will be noted that I have made no reference to the passage of large molecular substances into or out of the joint cavity. We are, as yet, only at the very beginning of our knowledge on this topic. Rather, have I tried to review the physical and chemical characteristics of synovial mucin, an important constituent of the joint fluid, and in such a way that the physiological importance of this substance might be illuminated and its relation to the pathology of joint diseases be rendered at any rate suggestive.

Mucin is a normal product of connective tissue, where no doubt it subserves several functions. It appears to be an intercellular cement, to regulate ionic distribution and osmotic equilibria, and to impart resiliency to the subcutaneous matrix. Its abundance appears to be affected to some extent by hormonal influences, and it is an intriguing possibility that the loss of resilience and the relative dehydration of the subcutaneous tissues which occur in old age are associated with a decrease in mucin content. Halliburton found in 1888 that the concentration of mucin is higher in the skin of children than of adults. If such changes take place with age in the subcutaneous connective tissues, is it not possible also that the degenerative changes which unhappily occur so frequently in the joints in old age may be related to changes in the quantity or quality of the synovial mucin which lubricates them ?

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La Mucine dans le Liquide Synovial

RÉSUMÉ

L'auteur tente de passer en revue les caractères physiques et chimiques de la mucine synoviale, constituant important du liquide articulaire, dans le but de mettre en lumière son importance physiologique, et il suggère une relation entre cette mucine et la pathologie articulaire. La mucine est un produit normal du tissu conjonctif dans lequel ses fonctions sont certainement multiples. Elle parait constituer un ciment intercellulaire, contrôler la distribution des ions et les équilibres osmotiques, et donner de l'élasticité à la matrice sous-cutanée. Son abondance semble être influencée par les hormones, et il est possible que la perte d'élasticité et la déshydratation relative des tissus sous-cutanés présentes chez les vieillards soient en relation avec une diminution de la quantité de mucine.

HISTOPATHOLOGY OF THE INTRINSIC MUSCLES OF THE HAND IN RHEUMATOID ARTHRITIS: A CLINICO-PATHOLOGICAL STUDY

BY

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New York

Since 1944 the author has systematically removed specimens from the intrinsic muscles of the hand whenever there was an occasion to reconstruct the painful arthritic hand (Kestler, 1946). This study is based upon eleven cases in which the intrinsic apparatus of the hand was studied under the microscope. In nine cases other tissues, including muscles, were examined from various regions of the skeletal system. Four controls were used who had been operated upon for traumatic lesions of their hands. It seems that sufficient data have been collected to report the findings.

The purpose of this article is to describe the pathologic changes found by the author in hands that were affected by rheumatoid arthritis in various stages of the disease. The impression is conveyed that rheumatoid arthritis is primarily a disease of the soft structures, the connective tissues proper. With the pathologic findings at hand the author's theory about the mechanism of specific deformity of rheumatoid hands will be advanced. The author is not aware of similar findings in the literature. Studies pertaining to the pathology of the intrinsic muscles of the hand in rheumatoid arthritis could not be found in a survey of the medical literature.

Literature

Koeppen (1932) appears to be the first to have found perivascular lymphocytic infiltration in the sciatic nerve in two cases out of eight which were examined. These were cases of acute or subacute rheumatism.

Curtis and Pollard (1940) described perivascular lymphatic infiltration in the skin and in skeletal muscles other than discussed in this paper. However, they called attention to the fact that these changes should be evidence of a generalized process.

In 1942 Freund and others reported lesions in the peripheral nerves in cases of rheumatoid arthritis. In a further study by the same authors (1945). inflammatory lesions were noted in the deltoid, triceps, and gastrocnemius muscles in fourteen patients with rheumatoid arthritis. These changes were unassociated with nerve fibrils.

Steiner and others (1946) confirmed their findings in a subsequent publication in 1946. Triceps, deltoid, pectoralis major, rectus abdominis, iliopsoas, gastrocnemius, and other unidentified muscles of the legs were examined at this time.

Gibson and others (1946) studied muscle material in eleven patients with generalized arthritis. These authors studied biopsy specimens from the deltoid, vastus externus and internus, and in one case from the biceps.

Aim of Study

When the author performed his first operation for a painful arthritic hand he was struck by the acuteness of the pathologic findings in spite of the very active so-called anti-rheumatoid therapy the patient had gone through, not only for years, but until shortly before surgery was undertaken. Besides several courses of gold therapy, this patient received the following treatments over a period of four years: antistreptococcus toxin, intravenous cinchophen, a non-specific vaccine, foreign protein, vitamin E, large doses of vitamin D, oral and parenteral salicylates, sodium iodide, and local and intravenous histamine. And yet the subcutaneous tissues were oedematous and inflamed. The capsule of the metacarpo-phalangeal joints was thickened and when it was opened a creamy greyish fluid escaped. The lining of the capsule had a dark red velvety appearance and consisted of enlarged villous tissue. Similar findings were encountered in practically every other case where the above structure was operated upon. The muscle bellies of the interossei, lumbricales, and those of the intrinsic

muscles of thumb and little finger, conversely, presented a normal gross appearance.

Another point of interest was that the characteristic deformity of the rheumatoid hand—the atrophy of the interossei, the ulnar deviation of the fingers in about 50 per cent. of the cases, the various fixed deformities of the phalanges—could not be entirely explained on the basis of disuse atrophy and gravity.

Material and Methods

Eleven patients with rheumatoid polyarthritis were operated upon. Different procedures were carried out, a great number of which were concerned with the metacarpo-phalangeal joints (Kestler, 1946 and in the press). The following structures were examined by biopsy: subcutaneous tissues, fascia, aponeurosis, extensor apparatus, para-articular and peri-articular tissues, capsule of metacarpo-phalangeal joints, capsule of interphalangeal joints, tendon sheaths, interosseous muscles, lumbricales, lateral bands. Tissues were excised under general anaesthesia and fixed in formalin. Blocks were cut in the normal way and paraffin embedding was used. Staining in every case was by haematoxylin and eosin; in some instances Van Gieson's and Weigert's methods were also used.

Case Reports

Since all these cases represented the characteristic lesions of rheumatoid polyarthritis, four will be described in detail.

Case 1

A housewife, 45 years old, had typical rheumatoid polyarthritis. With the exception of the spine and hip joints, every joint was involved over a period of nine years. The onset was gradual. Hands, elbows, and ankles were the areas of chief complaint when this patient was seen first in November 1943. Her general condition was fair. She was walking with a considerable limp due to the painful lesion in both ankle joints and in the tarsal and subtalar joints. Temporo-mandibular joints were subsequently involved, and shoulders, elbows, and wrists were restricted in their motions. There was a painful bursitis in both olecranon bursae, with fluid and thickening. Hip and knee movements were free and painless. Swelling and pain of both hands and feet were the principal complaints, and it was this latter condition for which the patient received several courses of gold therapy during the previous two years without any lasting effect.

It is of interest that this patient's ankles (the talar and subtalar joints) showed a most satisfactory and lasting response to histamine iontophoresis. The hands and more specifically the finger joints became increasingly painful. While every finger joint was painful and swollen, it was the proximal finger joint of each finger that was the centre of the complaints. When the pain became incessant the patient was hospitalized.

Examination of Hands.—A painful deformity of the metacarpo-phalangeal joints dominated the picture. These proximal finger joints were in 15° of flexion, from which active flexion was possible to 25°. Passively and with great pain this could be increased by 5°. The para- and periarticular tissues were enlarged and oedematous; the creases about the proximal finger joints were stretched. The middle finger joints of each finger were enlarged, and were held in moderate flexion. Motion in these joints was limited actively as well as passively. The distal finger joints were the least affected. The patient could not make a fist; pinching with the thumb and index finger and between thumb and mid-finger was weak. There was a moderate interosseous type of atrophy with ulnar deviation of the fingers on both hands. There was subluxation of all proximal finger joints.

Radiographs revealed the usual picture of atrophic changes with marked subluxations of the proximal phalanges in the proximal finger joints. The subluxation increased in degree from the index to the little finger.

The Wassermann reaction was negative; the blood sedimentation rate was 90 mm. in one hour (Westergren). There was an increase of serum globulin with the albumin-globulin ratio slightly reversed. There was moderate anaemia present. Blood uric acid was 3·8 mg. per 100 c.cm. Cholesterol and free cholesterin was normal. Kidney function was not impaired.

The excision of the metacarpal heads was performed as reported elsewhere (Kestler, 1946).

Gross Pathology.—Subcutaneous tissues were oedematous and injected. The extensor assembly was thickened, dark red, and the extensor tendons were found to be injected with a network of minute vessels; this was more marked at the periphery of the tendon. The extensor aponeurosis was dark red and thickened and, in spite of the pneumatic tourniquet, there was considerable ooze. The cut surface of the aponeurosis was enlarged in places. The articular capsule was greatly thickened and dark red. Upon incision of the joint, greyish material escaped from it. The synovia and articular surface of the joint capsule were bulging like a turned out sleeve, with an enormous villous thickening. The villi and the capsule were dark red. The articular cartilage was preserved, though injected, and there was a spotty pannus erosion throughout, particularly on the fourth and fifth metacarpal heads. This pannus erosion was limited to the periphery of the cartilaginous head. The interosseous muscles were normal in their gross appearance. The lumbricales were not inspected in their entirety, specimens being removed only after the metacarpal heads were excised. The lateral bands were dissected out on the index and mid-fingers. They were found to be injected and a thin film of inflammatory membrane was seen on them. This thin film of material could be seen on the extensor aponeurosis also.

The following tissues were examined: subcutaneous tissue, dorsal aponeurosis or extensor assembly, joint capsule, synovial membrane, cartilage cup, metacarpal head, dorsal interosseous muscles, lateral bands of intrinsic muscles, lumbricales.

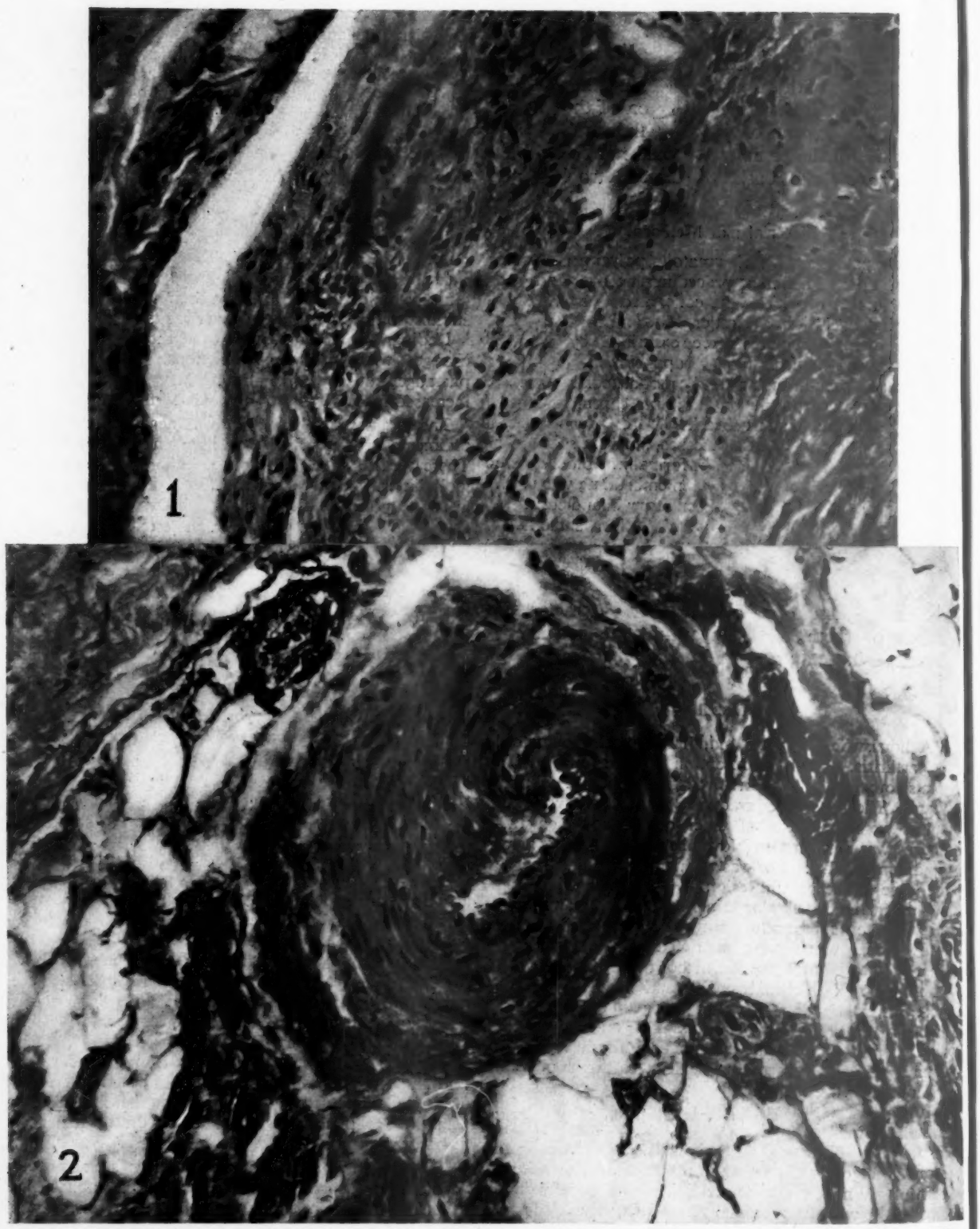
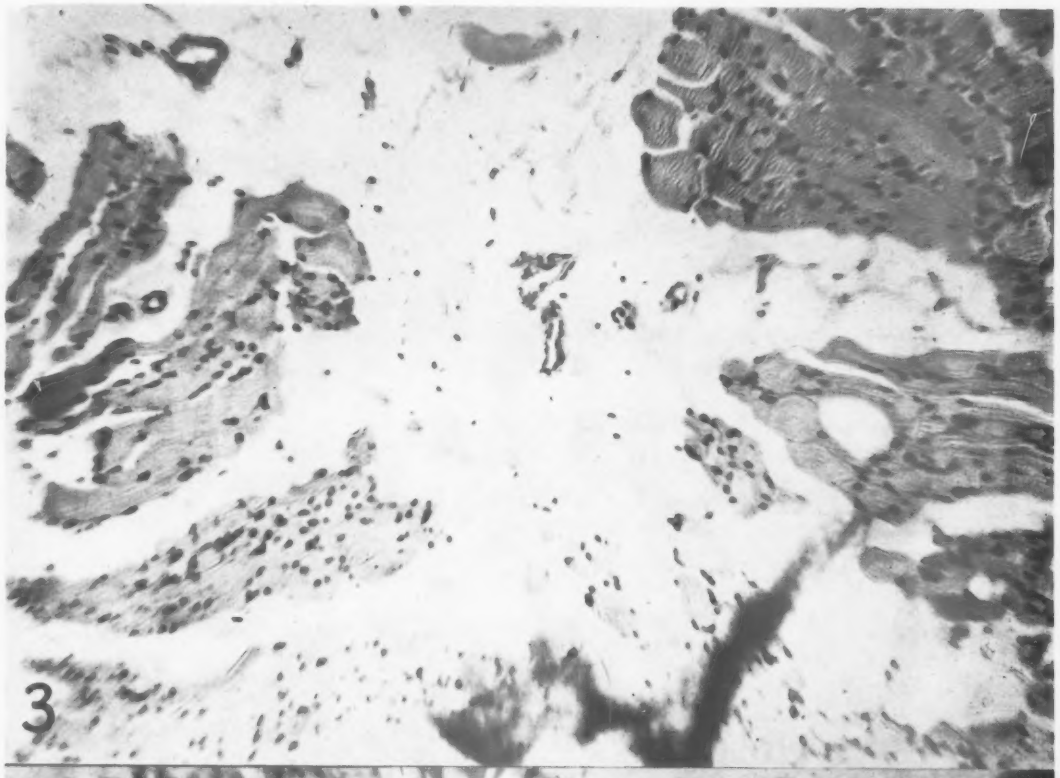


FIG. 1.—From extensor assembly, Case 1. Left long finger area showing the histology of a rheumatoid node. ×100.

FIG. 2.—From tissue removed with the capsule of proximal finger joint. This shows an extremely thickened arteriole, the lumen almost completely obstructed. In the right upper corner there is a circumscribed area of round-cell infiltration and above the vessel there is a more scattered round-cell infiltration. Both these are rather para-adventitially located. The fibro-collagenous tissue is abundant. ×400.



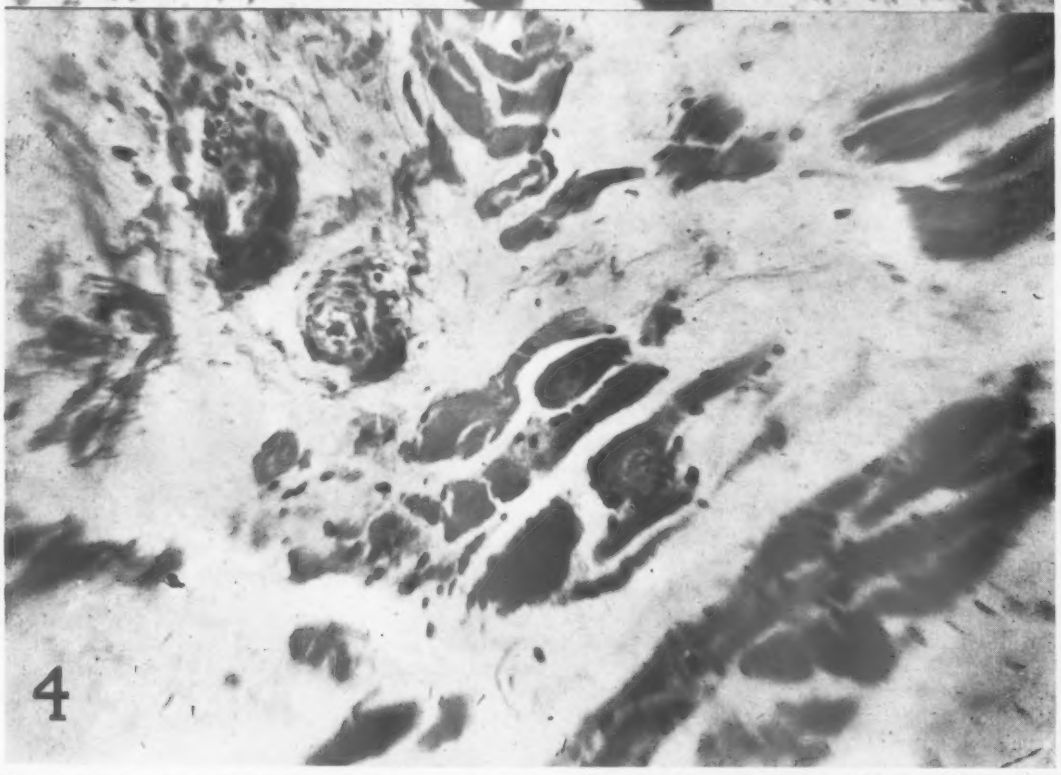


FIG. 3.—From first dorsal interosseous muscle, Case 1. Showing bizarre picture of inflammatory and degenerative changes. Increased amount of nuclei, scattered infiltration by round cells, cross striations in muscle fibres, shrinkage of muscle fibres. Connective-tissue mesh surrounding the areas where muscle tissue used to be. ×100.

FIG. 4.—From the second dorsal interosseous muscle, Case 1. Extreme stages of shrinkage of muscle fibres and scattered round-cell infiltration. Replacement of muscle tissue by collagenous fibres. Arterial changes within the muscle tissue and inflammatory changes in the blood vessel. On the left upper corner disintegrating muscle bundles are being replaced by connective tissues. ×250.

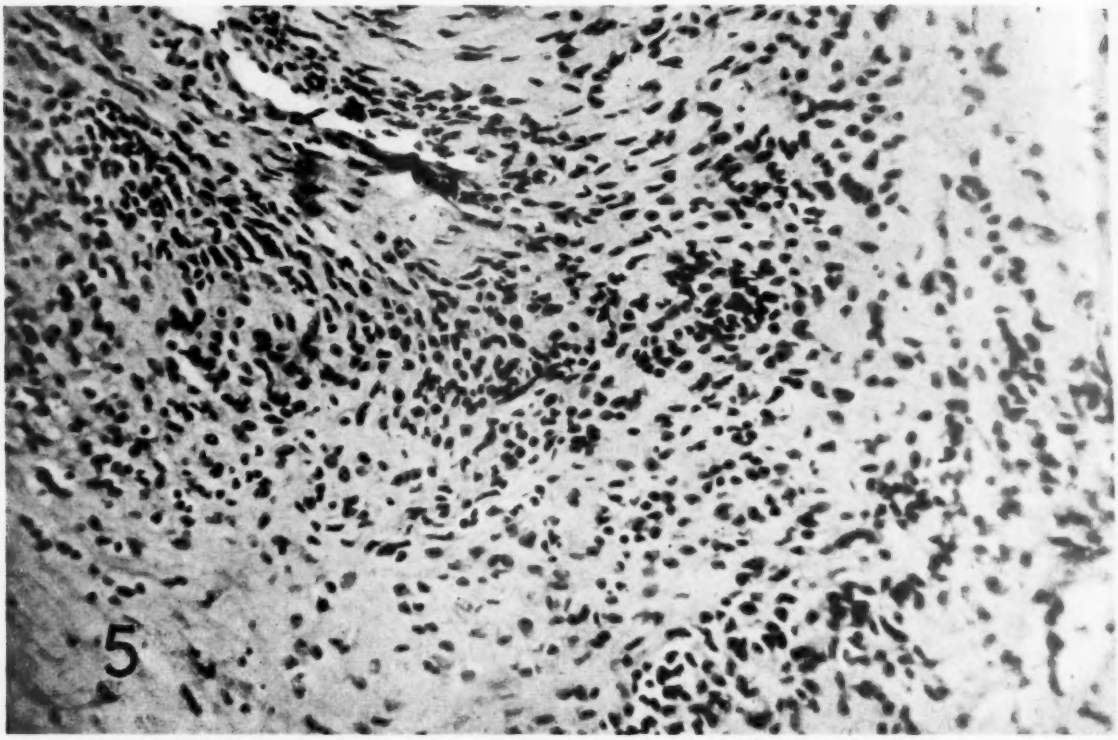


FIG. 5.—From the lateral band of the left index finger, Case 1. Showing histologic picture in a field from a lateral band. Diffuse infiltration by lymphocytes, epitheloid, and plasma cells in an abundant connective-tissue stroma. ×100.

Histological Findings

Subcutaneous Tissue.—In the subcutaneous tissue a scattered round-cell infiltration was found consisting mostly of lymphocytes. This round-cell infiltration occasionally showed a nodular appearance. Plasma cells were seldom seen in these areas; eosinophils were also few in number. Thickened arterioles and venules were seen occasionally and there was a round-cell infiltration occasionally observed para-adventitially.

Extensor Apparatus.—In the extensor apparatus diffuse infiltration with so-called rheumatoid pannus was found with epitheloid cells. plasma cells, and an increased amount of connective tissue. Numerous areas were found giving the picture of a rheumatoid node as seen in the subcutaneous nodes of rheumatoid individuals: a homogenous central area representing a necrotic field. This necrotic area showed different staining qualities. It consisted of necrotic connective tissue and was surrounded by epitheloid cells lying in a connective tissue stroma. These epitheloid cells were scattered with lymphocytes and plasma cells throughout (Fig. 1).

Joint Capsule.—The joint capsule showed a typical picture of a thoroughly homogenous rheumatoid granulation tissue with large numbers of lymphocytes and a great many plasma and epitheloid cells. The fibrocollagenous tissues were abundant. A small number of eosinophils were seen occasionally. Vascular changes were most interesting here. They consisted of extreme thickening of arterioles in places, with almost complete obliteration of the lumen (Fig. 2). There was a round-cell infiltration in the adventitia of these vessels.

The appearance of some of these arterioles showed a striking resemblance to findings in periarteritis nodosa. While there was no sign of cell infiltration of the intima or intramural tissue, the increase of collagenous tissue rich in cells was quite impressive.

Synovial.—Excessive villous hypertrophy with nodular inflammatory changes consisting of lymphocytes and plasma cells mostly, but there were also eosinophils. In the subsynovial tissues the blood vessels were increased and their wall was thickened. Inflammatory foci, nodular or diffuse in form, of scattered round cells were seen in numerous fields.

Cartilage Cup.—Grossly the cartilage cups were not very much affected. The centre of the head was intact; at the periphery there was pannus erosion in places. Microscopically it was seen that the metacarpal head was actually invaded by pannus and the cartilaginous surface eroded. In these eroded areas the cartilage matrix was loose; it showed signs of disintegration and the cartilage cells were fragmented and the nuclei had disappeared. The connective tissue, infiltrated throughout with cells, was invading the cartilage from outside and

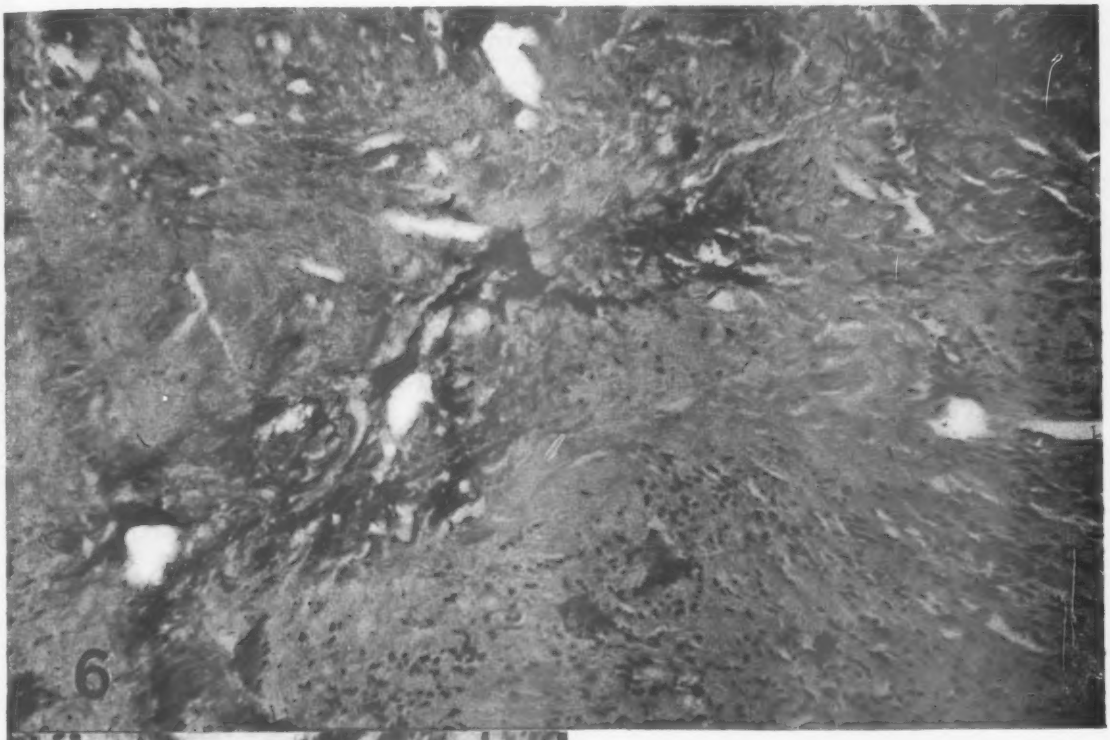


FIG. 6.—From the lateral band of the right index finger, Case 2. Showing central area of necrosis surrounded by epitheloid cells and lymphocytes (plasma cells). Great increase in connective tissue. ×100.

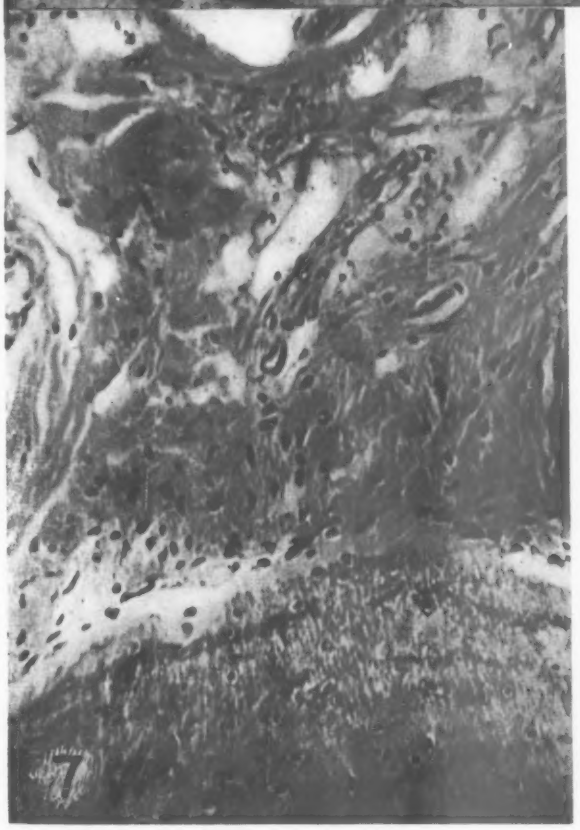


FIG. 7.—Section from the metacarpal head of the right mid-finger, Case 2. Pannus consisting of connective-tissue that is swollen in place and sclerotic in other areas, speckled by epitheloid cells and lymphocytes are invading the cartilaginous surface of the metacarpal head. This section is taken from the periphery of the cartilage cup near to the neck of the metacarpal bone. The cartilage itself shows signs of disintegration. ×100.

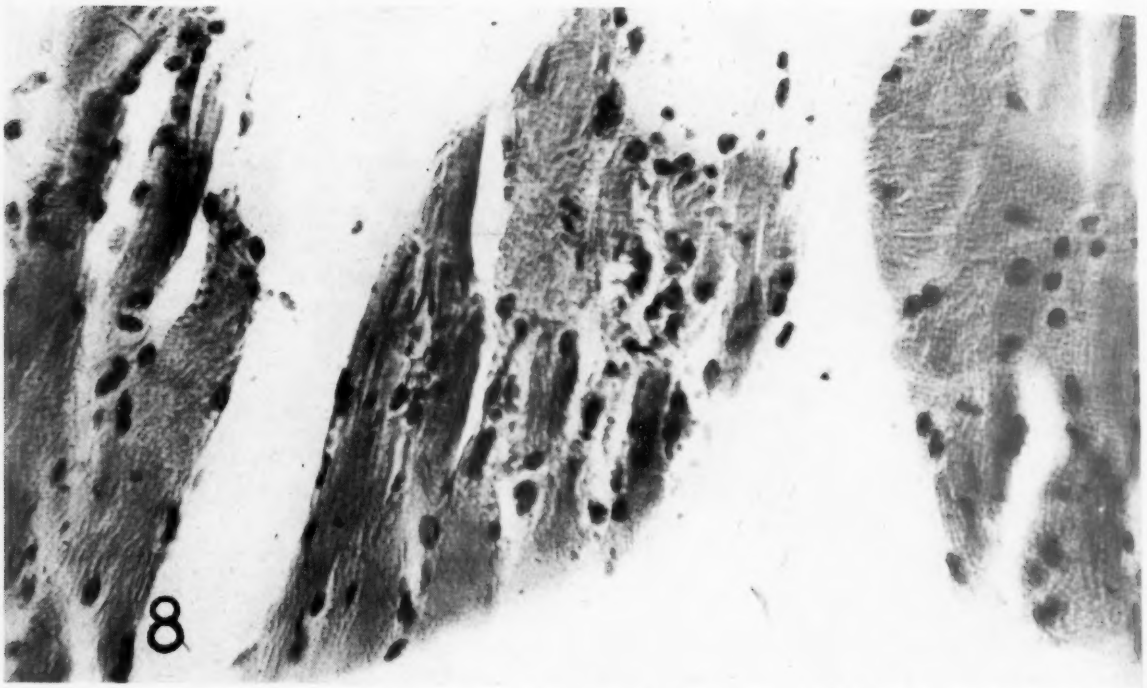


FIG. 8.—From interosseous muscle, Case 3. Extensive degenerative and inflammatory changes in the interosseous muscle. Approx. × 400.

finally eroded it. In this connective tissue a large number of minute capillaries were seen with their walls greatly thickened. A small number of lymphocytes were seen in their adventitia and not infrequently in their lumen. In the cartilage itself the following changes were seen. In the matrix there were areas of different staining. This was not due to the inequality of the slide in thickness. This we believe is a degenerative change which shows the following variations: thickening and fibrillation of the matrix as it goes into decomposition; the cartilage cells increase in number, their nucleus becomes large and plump; there is usually one nucleus; in areas where the number of cartilage cells is large they have lost their hyaline cartilage cell character, showing the structure of fibrocartilage; as the cartilaginous layer is thinning out it shows a longitudinal waving line staining dark blue.

Metacarpal Head.—The cortex was thinned out, the trabeculae were narrowed. In the marrow spaces, collections of lymphocytes and plasma cells were observed. These were frequently seen around blood vessels. One gained the impression that these changes destroyed the cartilage from within: the cartilage being pressed from the outside and from within the bone marrow by the granulation tissue. Similar observations were made by Bennett (1941) in other joints.

Muscles: *Interossei and Lumbricales.*—The most striking picture that was encountered by us in the study of the intrinsic apparatus of the hands was the diffuse involvement of the muscle tissue proper by inflammatory and degenerative changes.

An endomysial and perimysial round-cell infiltration was present, scattered all over in the various fields of slides. In places this was nodular in character as described by Steiner and others; however, there were many fields seen where these inflammatory lesions presented a more diffuse infiltration. The cells were mostly lymphocytes and epitheloid cells in this case. Plasma cells, mononuclears, and eosinophils were comparatively few. The shape of the nodules was various, spindle-shaped and elongated forms representing the majority. Most of the nodules seen in this area were not packed with cells but were rather interwoven by collagenous fibres. Quite interesting blood-vessel changes were found in the connective tissue between the muscle bundles, consisting of arterioles and capillaries with greatly thickened walls and with inflammatory cells in or near the adventitia (Fig. 4).

The muscle nuclei were greatly increased, their shape was elliptical or round and enlarged. The muscle fibres showed unusual shapes: wavy, crumbled, broken fibres mingling with normal ones. Abnormal transverse striations were seen in places, scattered holes in others. In some fields the transversely cut muscle bundles were missing and a fibrous mesh surrounded the shells of previous muscle tissue, representing fatty degeneration (Fig. 3). In other fields the disintegration and dissolution of muscle fibres could be observed and their replacement by collagenous tissue (Fig. 4). Perinuclear vacuolization was very frequent.

Lateral Bands.—Small specimens were removed from the lateral bands of the intrinsic muscles. There were

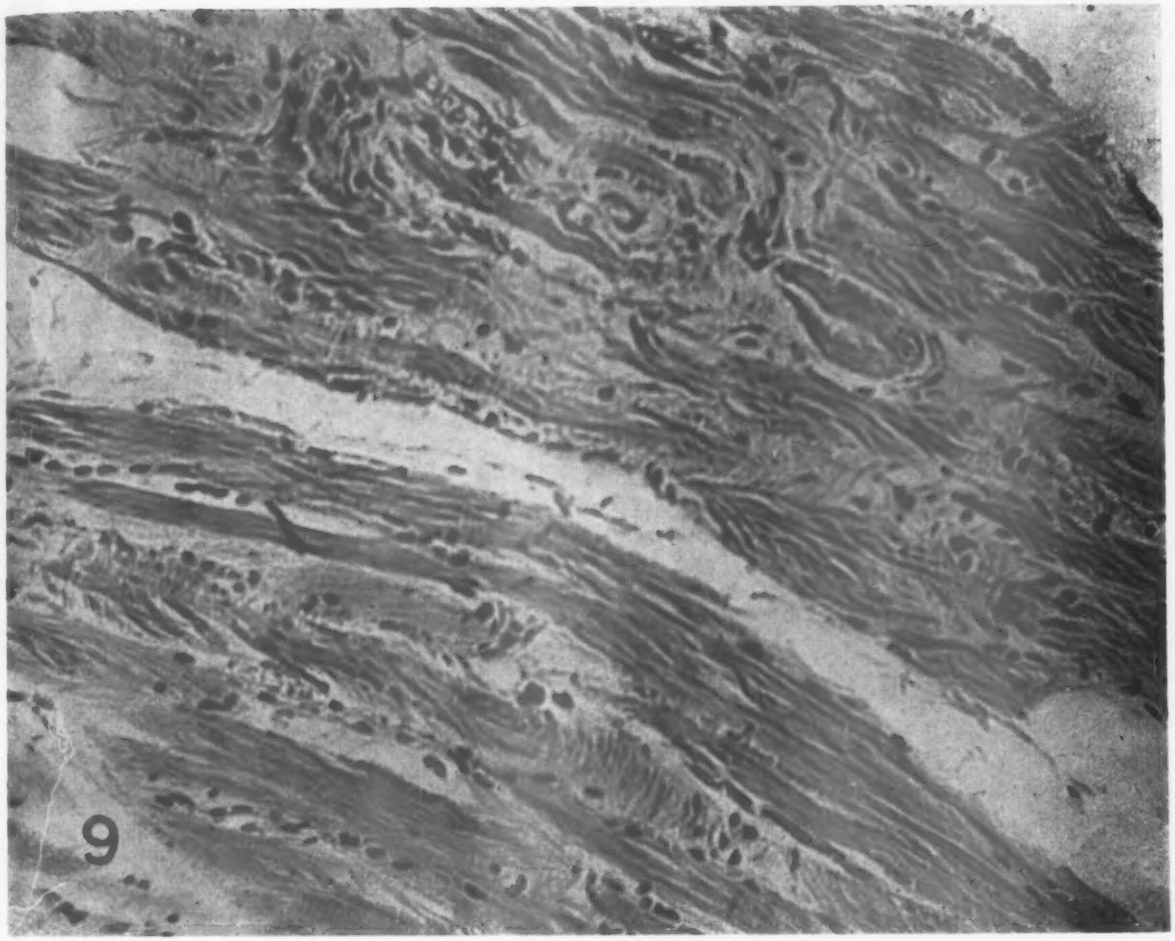


FIG. 9.—Section from lumbricalis muscle (second lumbricalis left hand), Case 4. Inflammatory and degenerative changes in the muscle tissue proper. ×100.

numerous fields infiltrated by epitheloid cells, lymphocytes, and plasma cells in a homogenous connective-tissue stroma. In places this infiltration has a nodular form (Fig. 5). There were fields that showed the characteristic appearance of the rheumatoid node.

CASE 2

A housewife, 42 years old, had suffered from rheumatoid polyarthritis for the past twelve years. Every joint of the body was involved, from the temporo-mandibular to the first metacarpo-phalangeal. There was extensive involvement of both hips with almost complete ankylosis. When she was seen at first, early in 1946, the sites of the patient's chief complaints were, in the following order: metacarpo-phalangeal joints of both index fingers, mid-finger joints of both mid-fingers, both hips, and both shoulders. The patient had been previously subjected to the usual anti-rheumatic treatments, including salicylates, bee venom, gold (three courses), vitamin D in large doses, and diathermy.

Right Hand.—There was moderate atrophy of the intrinsic muscles, with no deviation of the fingers in any direction. There was moderate swelling of the metacarpo-phalangeal joints of the index fingers only. Active extension of the metacarpo-phalangeal joint was possible to 170° with pain at this limit, and active flexion to 130°. Ten more degrees could be obtained by force, however, with great pain. No subluxation was present. Mid- and distal finger joints were intact. There was a similar condition of the left hand. The third fingers were practically intact. There was painful flexion deformity of mid-finger joints of both ring fingers with subluxation of the proximal portion of the mid phalanx.

The proximal finger joints of the index fingers being the centre of complaint, they were operated upon first (June 1, 1946). The metacarpal heads were excised as reported elsewhere (Kestler, 1946). Several biopsies were secured. Biopsy of lumbrical muscles was usually taken after the metacarpal head had been excised.

The Wassermann reaction was negative. The sedimentation rate was 45 mm. in one hour (Westergren).

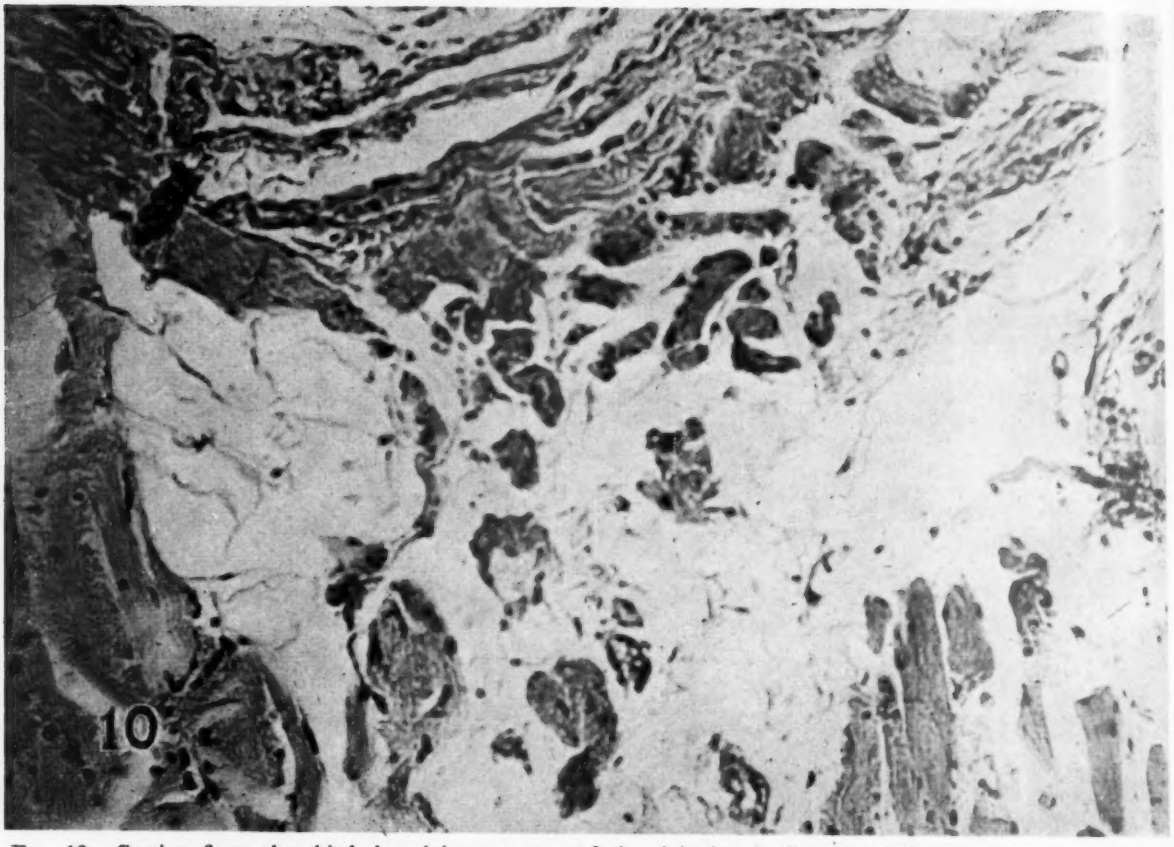


FIG. 10.—Section from the third dorsal interosseous of the right hand, Case 5. Inflammatory and extreme degenerative changes in interosseous muscle. ×100.

Except for moderate increase in serum globulin and moderate secondary anaemia, the rest of the findings were negative.

Radiographs revealed diffuse osteoporosis of the metacarpal bones and phalanges. There was no subluxation in any of the proximal finger joints.

Microscopic Findings.—Specimens of the tissues, as in Case 1, were examined and the results were about the same. The muscle involvement was less extensive, consisting only of spotty areas of inflammatory changes and similar degenerate changes. The interesting finding in this case was that sections taken from the lateral band of the intrinsic muscle of the left index finger showed the typical appearance of a rheumatoid node with an area of necrosis surrounded by epitheloid cells, plasma cells, and lymphocytes (Fig. 6).

While the radiographs did not reveal extensive bony changes and there was no subluxation, it is interesting to stress that, even in a case with mild clinical findings, tissue pathology was quite extensive. There was a visible thickening of the synovial membrane, mostly at the periphery of the cartilage cup; it showed a villous hypertrophy. In some places there was pannus erosion of the cartilage at the periphery.

This was considered a mild case both from clinical and pathological points of view. The follow-up confirmed this, inasmuch as two years after the operation there has been no recurrence of pain or swelling in the fingers that were operated upon, and there is the maximum functional result one can expect from this operation: active extension to 170° and full range of flexion in the proximal finger joint of the index finger. The pinching power of the index finger and thumb is good enough for most of the functional requirements.

CASE 3

A housewife, 34 years old, had had rheumatoid polyarthritis for nine years. The habitus was one frequently seen in patients suffering from this disease. Her family and past histories were not significant. The patient received most of the accepted anti-rheumatic treatments, including several courses of gold therapy to which she responded fairly well. The last course of chrysotherapy was given in 1946. Examination showed a fairly well-developed white female. Her general appearance was that of a chronically ill patient. Her weight was 118 lb. and her height 5 ft. 4 in. From the temporo-mandibular joints to the ankles, every joint was involved to a greater or less degree. The joints most

severely affected were both wrists and the periarticular and articular structures of both hands. While the lower extremities were involved, fairly good function was preserved.

The sedimentation rate was 28 mm. in one hour (Westergren). Red blood cells numbered 3,900,000 and white cells 7,400 per c.mm. of blood, and Hb was 75 per cent. Serum albumin was 3·8 per cent., serum globulin 2·9 per cent., and serum calcium 10·5 mg. per 100 c.cm. of blood. Alkaline phosphatase measured 3·9 Bodansky units. Serum phosphorus was 3·6 mg. and blood uric acid 3·1 mg. per 100 c.cm. of blood.

Right Hand.—This showed atrophy of the interossei to a very great extent. No ulnar deviation of the fingers was noticed. The thumb was markedly deformed, the distal phalanx was in the position of extreme hyperextension due to subluxation, and so was the proximal phalanx. There was painful limitation in the motion of the metacarpo-phalangeal joints; each had a different range, the fourth and fifth being the most painful. Each proximal phalanx was subluxated under the head of the respective metacarpal bone. There was an average of 20° flexion contracture in the metacarpo-phalangeal joints; active flexion from that point was possible to 35°. The patient was not able to make a fist.

Index Finger.—The middle finger joint was rigid in slight hyperextension. The distal finger joint of the index finger could be actively flexed from its normal extended position approximately 15°.

Mid-finger.—The middle finger joint was in about 15° of hyperextension with no active or passive flexion in this joint. The distal finger joint was not in flexion contracture but rather in the position of 10° of flexion from which passive extension was full and active flexion restricted.

Fourth and Fifth Fingers.—Changes in the fourth and fifth fingers were restricted mostly to the metacarpo-phalangeal joints with extensive subluxation and a considerable amount of pain in these joints. The deformity in the other finger joints of the fourth and fifth fingers was only moderate.

Tissue Pathology.—Subcutaneous tissues appeared to be normal in colour and thickness. The aponeurosis of the extensor apparatus as well as that of the intrinsic muscles was found to be thickened. Upon incision of the capsule of the proximal finger joints small amounts of light-greyish, thick fluid escaped. The lining of the capsule was oedematous and thick, and villous tissue was facing the joint cavity. The villi were enlarged and pinkish in colour. The articular cartilage of the second and third metacarpal bones was practically normal, which means that it was intact and had a shiny appearance but at the periphery of the cartilage cup the synovial membrane was thickened and red. These findings were very interesting in view of the fact that this patient had had a number of courses of gold therapy shortly before surgery. This finding was in accordance with findings we had in other cases that had had gold therapy and also in accordance with the findings of authors like Gibson and others. Specimens were removed from all the tissues encountered; then the interosseous muscles were carefully dissected out. They were normal in appearance, and somewhat pale. However, this may be due to the fact that a tourniquet was used. Specimens 0·5 cm. in length and 3 mm. in width were removed from two interossei, namely, those of the index and ring fingers. More advanced changes were found at the heads of the fourth and fifth metacarpals including their para- and periarticular tissues; the thickening was greater, the villi were larger, the subluxation more extensive, and the metacarpal heads were destroyed; the cartilage had disappeared and there were marginal exostoses at the epiarticular area.

Microscopic Findings.—The most striking findings in this case were the colourful variations of stages in muscle tissue proper, showing the wide variety of inflammatory changes and degenerative changes as described above (Fig. 8). Inflammatory changes about the blood vessels were also noticed within the mucle tissue. The findings were very much the same as in Cases 1 and 2 already described in detail.

The middle finger joint of the right mid-finger was also operated upon in this patient. Specimens from the joint capsule and ligaments as well as of the extensor expansions showed lesions similar to those in the proximal finger joints.

Case 4

A man, aged 44, had rheumatoid polyarthritis with an eleven-year history. All his joints were involved. The disease was in a quiescent stage with the exception of the finger joints of both hands. His sedimentation rate was 48 mm. (Westergren). He was anaemic. His albumin-globulin ratio was moderately reversed. Blood uric acid was 3·8 mg. per 100 c.cm. He had had many courses of gold therapy, the last three months ago. There was a response to gold therapy at the beginning but subsequently he had no improvement. He was seeking relief for painful limitation of the proximal finger joints on both hands.

Hands.—The neutral position of both hands was accentuated by an extensive ulnar deviation of the fingers. The area of the proximal finger joints was swollen; they were held in 15° of flexion; from this position there was about 10° of flexion possible with pain. All proximal phalanges were subluxated. The mid-finger joints were held in extension, and with the exception of the fourth and fifth fingers on both hands they could not be flexed. There was 15° flexion deformity of both distal finger joints of both index fingers. Because of extreme pain and limitation of motion, the excision of the metacarpal heads was performed.

Pathology.—The para- and periarticular tissues about the metacarpo-phalangeal joints were oedematous, and thickened. Upon opening the joint capsule a considerable amount of greyish fluid escaped. The lining of the capsule was thick; villous tissue was emerging from the synovial structures, which were dark red. The villi could be seen well by gross examination. The articular cartilages of the metacarpal bones were destroyed. The damage to them was increasingly severe from the index to the fifth finger; in other words, while

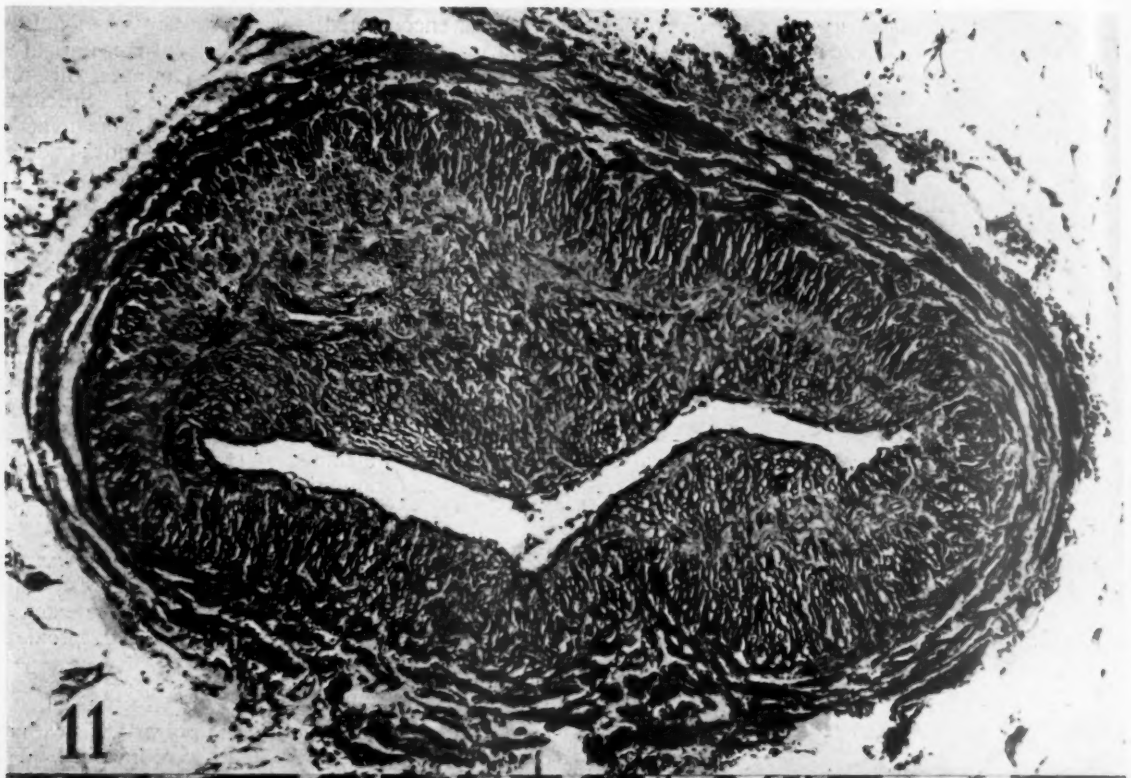
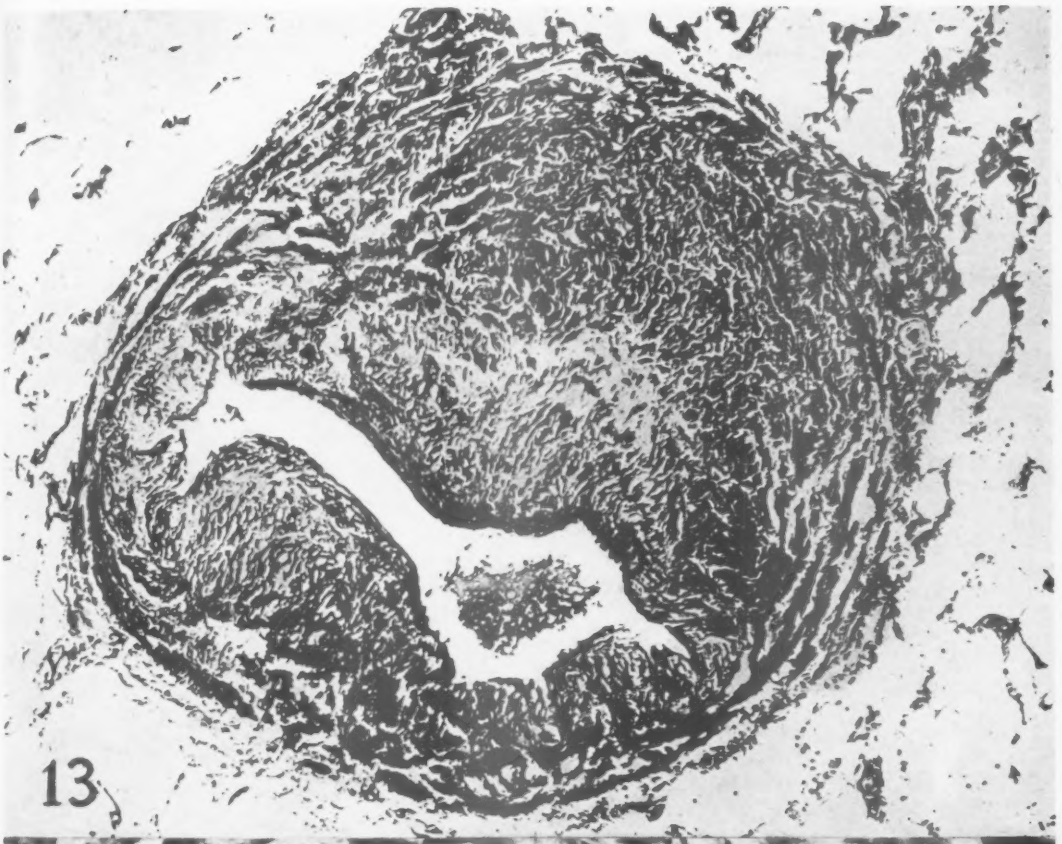


FIG. 11.—Blood vessels from intermuscular septum of left vastus lateralis, Case 5. Showing diffuse peri-adventitial round-cell infiltration. Extensive obliteration of the vessel is quite striking. ×150.

FIG. 12.—High power view of Fig. 11, showing excessive amount of fibro-collagenous tissues rather rich in cellular elements. Vacuolization of cells seems to be a significant feature. ×372.



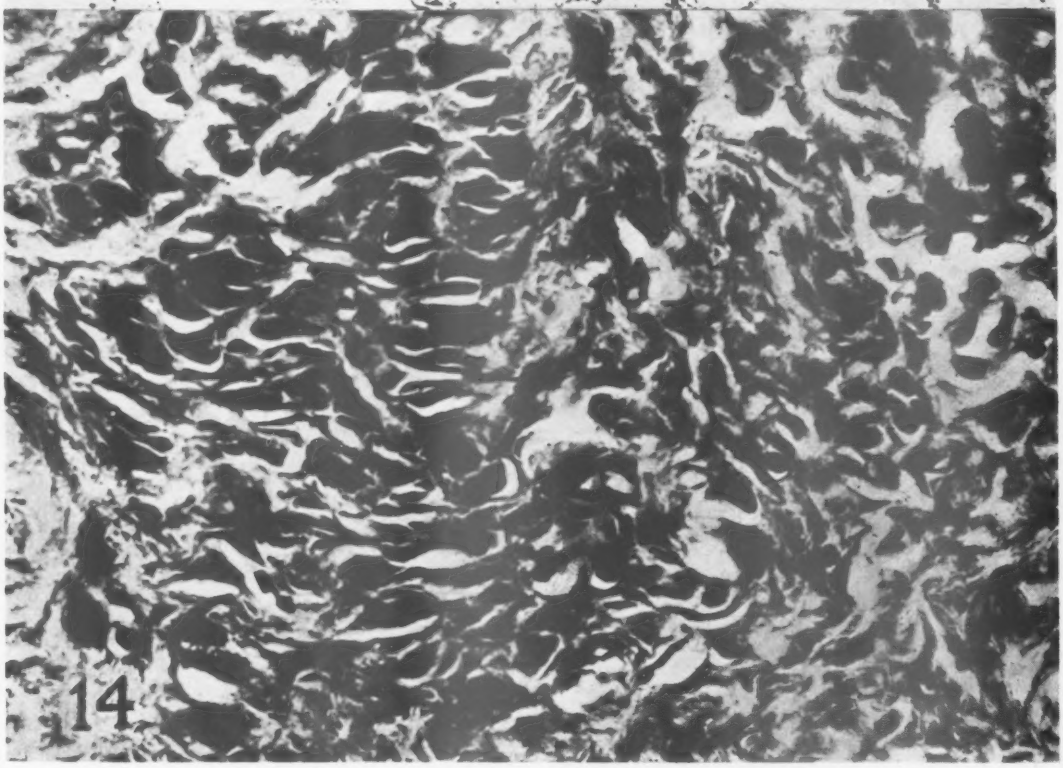


FIG. 13.—Blood vessel from intermuscular septum of right gluteus medius, Case 6. Showing extreme thickening of the blood vessel and scattered round-cell infiltration outside the vessel. ×150.

FIG. 14.—High-power view of Fig. 13. Fibro-collagenous changes similar to those in Fig. 12.

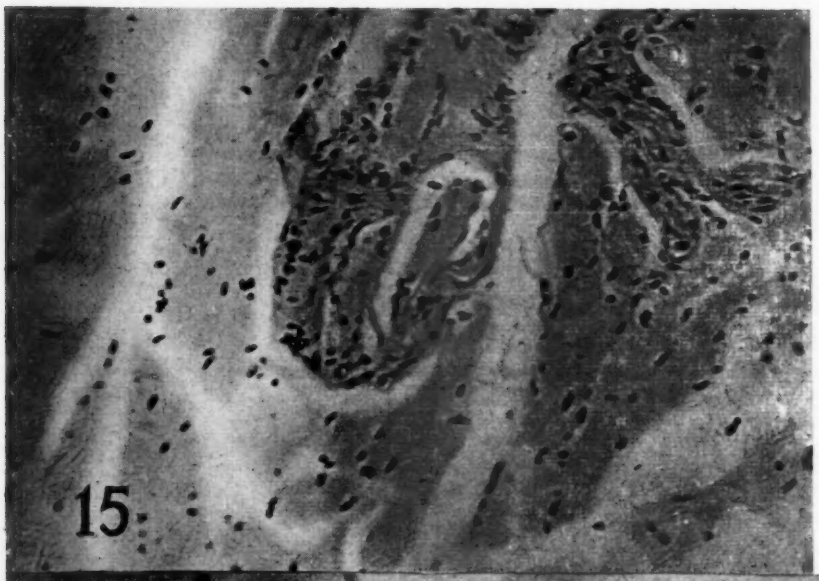


FIG. 15.—Lumbrical muscle, left hand, Case 7. ×250.

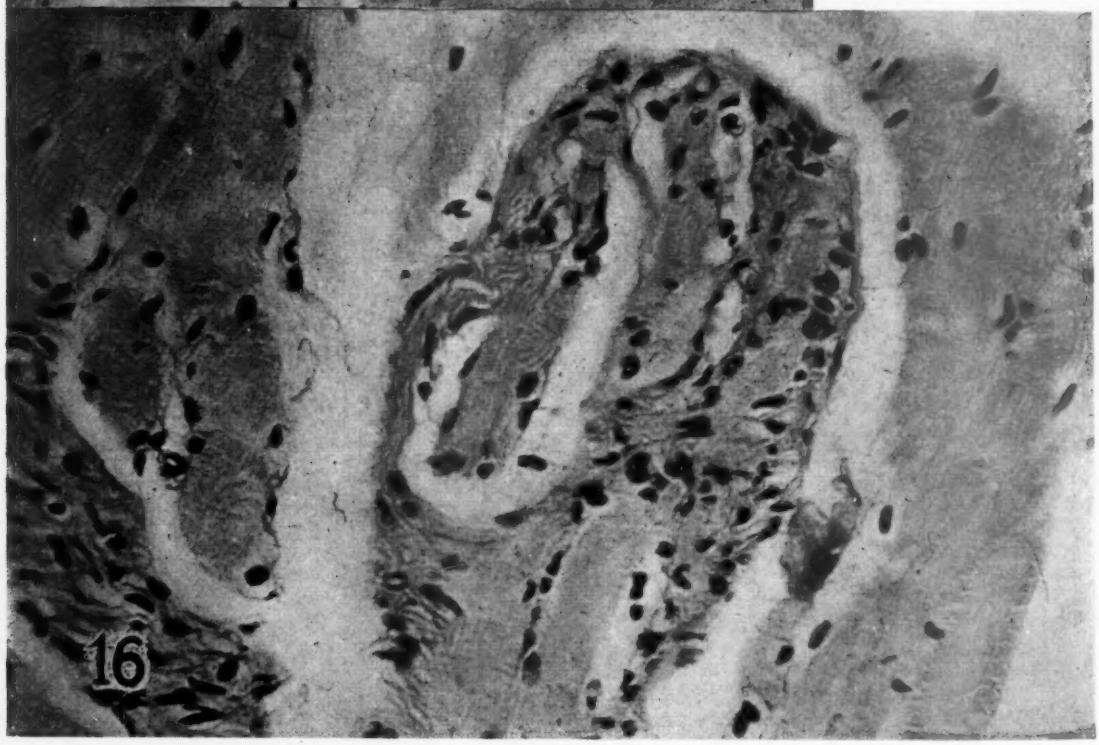


FIG. 16.—Same as Fig. 15. ×400.

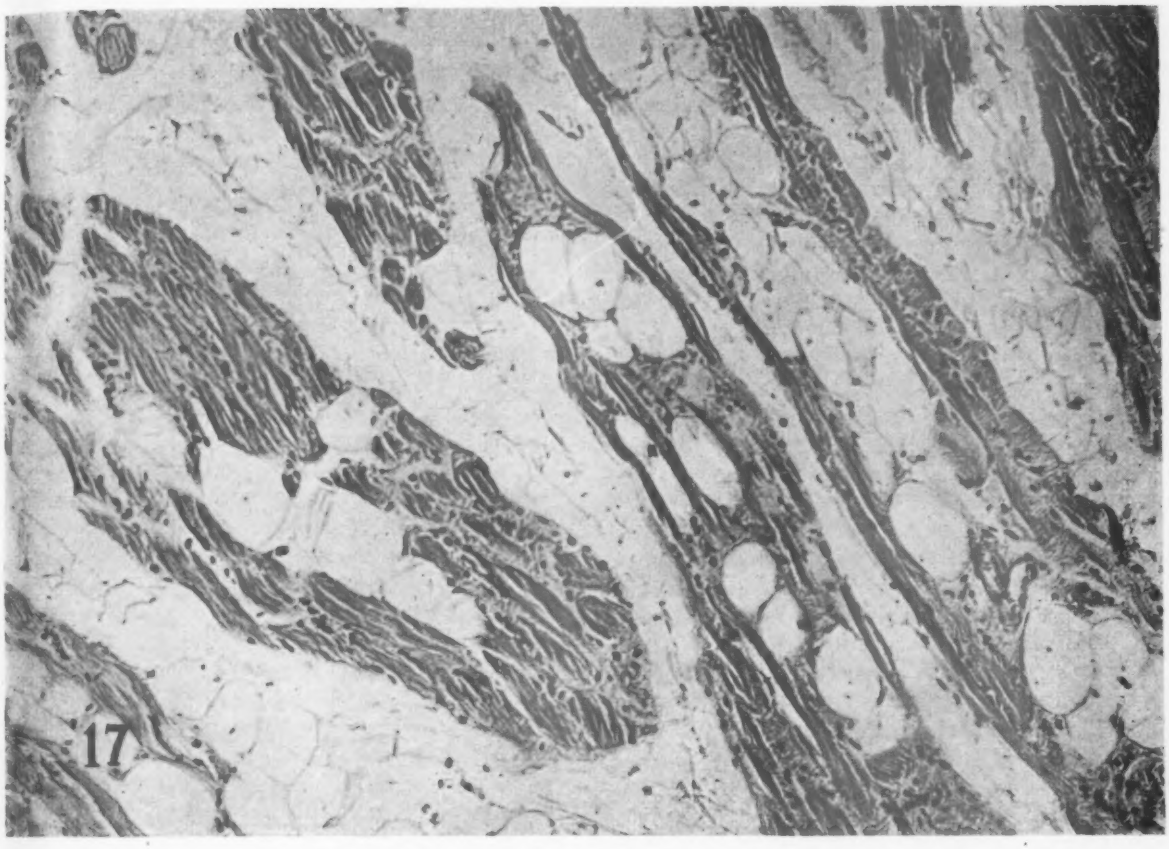


FIG. 17.—Interosseous muscle, Case 8. Extensive inflammatory and degenerative lesions in the muscle tissue proper. ×100.

there were cartilage islands on the second and third metacarpal heads; hardly any remained on the fourth and fifth.

Microscopic examination of tissues was performed by the same routine as in the previous cases. The findings were very similar to those seen in the previous cases (Fig. 9).

CASE 5

A 41-year-old woman with a history of rheumatoid polyarthritis of six years' duration had as the outstanding feature extreme changes in the dorsal third interosseous of the right hand (Fig. 10). Figs. 11 and 12 show significant blood vessel changes in the left vastus lateralis in this case.

CASE 6

A 37-year-old woman had rheumatoid polyarthritis of four years' duration. The details were practically the same as those reported for previous cases. The dorsal interosseous of the mid-finger of the right hand was found to be involved in numerous places, as shown in previous cases described above. Characteristic changes in the blood vessels were found in this case in other skeletal muscles (Figs. 13 and 14).

CASE 7

A 34-year-old man had rheumatoid polyarthritis for four years. Figs. 15 and 16 show change in one of the lumbrical muscles in the left hand.

CASE 8

A 29-year-old woman had rheumatoid polyarthritis of three years' duration. Fig. 17 represents a section from an interosseous muscle of the right hand. A section obtained from the metacarpal head of the right mid-finger revealed pannus eroding the cartilage cup in a similar way to that shown in Fig. 7. There was disintegration of cartilage tissue where the pannus invaded the cartilage.

CASE 9

A 48-year-old woman with rheumatoid polyarthritis of five years' duration showed findings practically identical with the ones previously described.

CASE 10

A 42-year-old man for the past eight years had been suffering from rheumatoid polyarthritis. Tissue changes did not differ from those reported above.

CASE 11

A 41-year-old woman had rheumatoid polyarthritis of six years' duration. The histopathology consisted of lesions similar to those in the previous cases.

Discussion of Tissue Pathology

In summarizing our findings in the intrinsic apparatus of the hand, the most striking feature was the active involvement of the extensor assembly, the muscle tissue proper, and the lateral bands by the rheumatoid process.

In the muscle tissue the lesions observed should be divided in four groups:

1. Inflammatory lesions. These were perimysial and endomysial in character. The cell elements consisted of lymphocytes, plasma cells, epitheloid cells, and much less extensively of mononuclear, eosinophil, and polymorph neutrophil cells. The arrangement of these cells was frequently nodular according to the description of Freund and others (1942) and Steiner and others (1946). However, a scattered infiltrative appearance was not infrequently observed.

2. Degenerative changes of muscle tissue represented by the enlargement of muscle nuclei, increase in number of the nuclei, vacuolization with eccentric position of the flattened nucleus, etc.

The muscle fibres took on a variety of abnormal shapes: winding and bending as a sign of shrinkage was observed. The shrunken muscle fibres were swollen and wavy. Muscle fibres were broken up into small elements: some of them showed a spotty disintegration; others were replaced by fatty or fibrous connective tissue.

3. Changes in the blood vessels were two-fold, thickening of their walls by concentric increase of collagenous tissue and a peri- or para-adventitial round-cell infiltration in these small blood vessels.

4. Collagenous tissue changes consisting of increase of the collagenous tissues and swelling of their ground substance. Fibrinoid changes in the connective tissue and sclerosis of the collagenous substance were observed. Where the degenerative changes in the muscle fibres were extensive, replacement by connective tissues was abundant.

We have already mentioned the concentrically thickened walls in the small blood vessels. It seems that this thickening is not confined to the adventitia only but also extends intramurally. The nodular and diffuse round-cell infiltration about the vessels was also referred to. These changes about the small blood vessels were observed in the extensor aponeurosis, in the subcutaneous tissues, in the joint capsules, and in the connective tissue septa of the muscle tissue proper.

It is not the aim of this paper to discuss similarities in histopathology of cases of rheumatic fever, scleroderma, periarteritis nodosa, and lupus erythematosus (Klemperer, 1947). We merely wish to record these findings in the intrinsic muscles of the hands of patients suffering from rheumatoid polyarthritis.

Structures Other than Muscle Tissue

In the extensor assembly and in the fibrous attachments of the intrinsic muscles like the lateral bands or the structures about these bands, rheumatoid granulation tissues represented by diffusely infiltrated connective tissue, by epitheloid cells, lymphocytes, plasma cells, occasionally by eosinophils, was the routine finding. A feature not described heretofore was the textbook picture of a so-called rheumatoid node right in these extensor expansions. The significant blood-vessel changes were observed in these structures as well.

Aetiology

From these findings we may conclude that rheumatoid arthritis is primarily the disease of the soft tissues, as stated by Gibson and others (1946), among others. A blood-borne infection, most likely an agent from the group that causes infectious granulomas, is invading the mesenchymal tissues. Of these mesenchymal tissues the connective tissues and muscles seem to be involved primarily. As to the articular cartilage, this is being invaded secondarily. Inflammatory changes in the bone marrow were observed by us and by others (Bennett, 1941). Pannus erosion of the articular cartilage is a common finding; it seems, therefore, that the articular cartilage is pounded from within and from outside.

Allergic reaction does not seem to explain, at least to us, the tissue reactions of rheumatoid arthritis. We are in agreement with those who are of the opinion that alterations in the connective tissue as described by us and by others (Klinge, 1933; Rossle, 1933; Schosnig, 1932; Wu, 1937) in different conditions are not necessarily of allergic origin. We know from the work of Schosnig, Wu, Selye and Pentz (1943), and others that fibrinoid collagen changes must not be interpreted invariably as an expression of allergic reaction. It is our unshaken belief that rheumatoid arthritis is not an allergic disease.

Correlation of Tissue Pathology with the Clinical Picture

It was a known fact that tendon sheaths, the synovial membrane, the articular cartilage, and the bone itself about the finger joints became actively

involved with rheumatoid granulation tissue. It was also a generally accepted view that the intrinsic muscles of the hand developed an atrophy of disuse.

Nothing is to be found in the literature, however, dealing with observations regarding the intrinsic apparatus itself: the extensor assembly, the interosseous and lumbrical apparatus, and their extensor expansions or lateral bands. Following the work of Freund and others, and again that of Steiner and others which dealt with what they described as a nodular polymyositis and neuromyositis of rheumatoid arthritis, it became quite possible that changes they found in skeletal muscles depicted at random may be found in muscles all over the body. And yet the active involvement of the intrinsic muscle apparatus in inflammatory lesions and the degenerative changes developing thereon offers an explanation for a number of clinical facts hitherto not appreciated.

It is not within the scope of this paper to elaborate on the evolutionary phases of the deformed arthritic hands. Another study is dealing with this problem in detail (Kestler, in the press). We are confined, therefore, to a few statements based upon the pathological findings as discussed above. While a basic pattern is almost invariably present the rheumatoid hands do not show a uniform deformity. The basic pattern applies to the proximal finger joints, which almost invariably show a flexion deformity. There are numerous variations, however, in the deformities of the middle and distal finger joints.

The basic factor responsible for the deformities is the active inflammatory involvement of the periarticular structures of the finger joints as well as the inflammatory and degenerative lesions of the intrinsic muscle apparatus proper. It is appreciated, however, that these inflamed, painful units of the hand are secondarily subjected to the force of gravity. Due to these inflammatory changes the intricate mechanism so important in maintaining the accurate balance of the intrinsic muscle apparatus is disturbed, and finally, as the condition progresses, completely lost.

Added to this, the inflammatory and degenerative changes in the muscles resulting in shrinkage and loss of muscle substance will shorten the muscles, producing thus an interosseous type of atrophy and an ulnar deviation of the fingers. The degree of this latter deformity seems to be dependent upon the amount of intact muscle tissue that has survived. This muscle tissue will then permit a more or less limited functional activity of the fingers.

The condition could be compared perhaps with the " fibrous contracture of the hand ", a clinical entity only recently described by Bunnell (1948). In this, due to entirely different aetiology, fibrous bands throw the intrinsic muscles out of action. In rheumatoid arthritis of the hands, the active inflammatory disease and the secondary degenerative changes of the muscle tissue itself and the fibrous attachments thereof are inhibiting and eliminating the active function of the intrinsic muscle apparatus.

Conclusions

In eleven cases of chronic rheumatoid polyarthritis which were treated by surgery, biopsy specimens taken during reconstruction of deformed hands revealed inflammatory and degenerative changes in the intrinsic muscles. Inflammatory and degenerative lesions were marked in all these cases.

Almost invariably the characteristic histologic appearance of the subcutaneous rheumatoid node could be observed in the aponeurotic sleeves, the lateral bands, the joint capsules of proximal and middle finger joints, and the tissues thereon. Frequently the inflammatory lesions were found to be nodular in character; however, diffuse infiltration of the tissues was just as frequent.

Significant lesions about the blood vessels are reported, mostly in the small arteries, consisting of concentric accumulation of connective tissues and of peri- and para-adventitial nodular foci. These arterial lesions showed similarities to the ones seen in periarteritis nodosa.

The opinion is expressed that the lesions in the structures described above, including the muscle tissue proper, are the primary ones. The articular cartilage seems to be affected by secondary invasion.

In five of the eleven cases, biopsy specimens were taken from other structures and muscles besides the hand, and similar lesions to those reported here were found.

Chrysotherapy did not seem to influence tissue pathology, regardless of the number of courses given and whether or not there was a favourable response. The time that had elapsed between removal of biopsy specimens and the discontinuance of chrysotherapy did not seem to modify the histopathology. Two cases which according to their histories were not subjected to gold therapy showed identical changes. In view of these findings, while the great value of chrysotherapy if successful is recognized, the conclusion is established that its effect is nothing but palliative. It cannot and does not directly hinder the growth of rheumatoid granulation tissue. It may, however, indirectly delay destruction of articular cartilage by permitting active function, rendering temporary relief in cases where this is done by the drug.

The characteristic deformity of the rheumatoid hand is the result of simultaneous factors, of which the primary and dominating feature is the direct involvement of the intrinsic muscle apparatus proper by the rheumatoid process. The wonderful precision balance of this intrinsic apparatus is disturbed through this, establishing the first link in a chain of pathological sequences.

According to our observations, active use of the hands and their finger joints seems to delay or even prevent destruction of these non-weight-bearing articulations.

It was observed that the amount of subluxation in the proximal finger joints increases from index to little finger. The destruction of the articular cartilage was found to be increased in the same manner.

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Histopathologie des Muscles Propres de la main dans l'Arthrite Rhumatismale; Étude Anatomo-clinique

Conclusions

Dans onze cas de polyarthrite rhumatismale chronique traités chirurgicalement, la biopsie pratiquée au cours de la reconstitution des mains déformées a révélé des modifications inflammatoires et dégénératives des muscles propres. Ces lésions inflammatoires et dégénératives étaient également marquées chez tous les malades.

On a presque invariablement observé l'apparition de nodules rhumatismaux sous-cutanés à aspect histologique typique, siégeant au niveau des gaines aponévrotiques, des ligaments latéraux, des capsules articulaires des articulations proximales et médiane des phalanges et des parties molles. Les lésions inflammatoires étaient fréquemment de caractère nodulaire; mais l'infiltration diffuse des tissus était tout aussi fréquente.

L'auteur rapporte la présence de lésions périvasculaires marquées, surtout dans les artérioles, et constituées par l'accumulation concentrique du tissu conjonctif et de foyers nodulaires péri- et para-adventitiels. Ces lésions artérielles présentaient des analogies avec celles que l'on observe dans la périartérite noueuse.

L'auteur exprime l'opinion que les lésions dans les structures décrites ci-dessus, y compris les tissus musculaires eux-mêmes, sont des lésions primaires. Le cartilage articulaire semble être affecté par l'invasion secondaire.

On a pratiqué la biopsie d'autres tissus en dehors de la main chez cinq malades sur onze, et l'on a observé des lésions semblables à celles qui viennent d'être décrites.

La chrysothérapie ne semble pas avoir eu une influence sur les lésions tissulaires, indépendemment du nombre des séries de traitements administrées, et quel qu'ait été le résultat clinique. Le temps écoulé entre la biopsie et la cessation du traitement ne semble pas avoir modifié l'aspect histopathologique. Deux malades qui, d'après leurs observations, n'avaient pas reçu de traitement par les sels d'or présentaient les mêmes modifications. Ces résultats amènent à conclure que, malgré sa valeur, la chrysothérapie ne produit qu'un effet palliatif. Elle ne peut pas empêcher directement la développement du tissu granuleux rhumatismal. Mais elle peut retarder indirectement la destruction du cartilage articulaire en permettant l'activité fonctionnelle, et en amenant un soulagement momentané dans les cas où ce résultat est obtenu par la médication.

La déformation caractéristique de la main rhumatismale est due à plusieurs facteurs simultanés qui sont essentiellement caractérisés par l'atteinte directe par le processus rhumatismal de l'appareil musculaire propre. Cette atteinte dérègle l'admirable appareil de précision constitué par les muscles de la main, et forme le premier élément d'une série de modifications pathologiques.

L'activité des articulations des mains et des doigts semble retarder ou même empêcher la destruction de ces articulations qui ne supportent pas de poids.

On a observé que le degré de luxation des articulations digitales augmente en allant de l'index au petit doigt. On a trouvé que la destruction du cartilage articulaire augmente dans le même sens.

THE CLINICAL SIGNIFICANCE AND TREATMENT OF LESIONS OF THE INTERVERTEBRAL DISK

BY

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The following discussion of the " disk problem ", although based upon a paper read before the Orthopaedic Section of the British Medical Association in June 1948, should be regarded as complementary to the anatomical and mechanical study of the lumbo-sacral region published previously in the *Annals of the Rheumatic Diseases* (Capener, 1944). My thesis is that, important as the retropulsion of an intervertebral disk may be in the causation of sciatica, nevertheless there is a large group of associated disturbances which merit a long course of conservative treatment before it is justified to carry out surgical intervention. The treatment that I am concerned to emphasize is the use of the plaster-jacket method of relative immobilization, associated with a carefully planned course of after-treatment by physical methods. I would go further, and say that we need also to consider some additional factors relating to the causation of lumbo-sacral derangements. I refer to fatigue and debility (both psychological and physical) which seem so prevalent at the present time; these factors may have an important bearing on their apparently greatly increased incidence today.

It is important that we should be clear about what we are discussing. The layman wants labels for the diseases he suffers from, and we medical men are driven to supply them. In our ignorance we apply such terms as sciatica, lumbago, rheumatism, fibrositis and, if we belong to a particular school of thought, we may even talk about osteopathic lesions. I would, however, like to ask whether the average doctor is any wiser when he sends a patient to hospital with the diagnosis of " disk lesion " or " slipped disk ". If, as we have been led to believe, such disturbances mean operation, then I think that we are doing our patients a great disservice by using such labels, which detract from the essential problems with which we have to deal. I will expose the looseness of the term " lesion of the intervertebral disk " (applied as it often is only to posterior protrusion of the disk) by the reminder that almost every pathological process affecting the spine involves, more or less, the intervertebral disks. This is particularly true of spinal tuberculosis, which is commonly mistaken, in its early stages, for such mechanical lesions of the intervertebral disks. The intervertebral disks are merely individual articulations of the spine and, as with the other joints of the body, have an equally varied pathology ranging from congenital anomalies, developmental disturbances, infective arthritis, chronic deforming arthritis, metabolic disorders, and traumatic defects, to neoplasms. The differential diagnosis of traumatic lesions of the intervertebral disk must consider all these possibilities as well as other disturbances of the vertebral skeleton, the spinal cord, the viscera, the rest of the locomotor system, and the brain; this is what makes the present subject so fascinating, yet nevertheless impossible of adequate discussion in the space here available.

Anatomy and Pathology

An important concept to grasp is that the intervertebral joints do not have the individuality of function that is possessed, say, by the hip joint or shoulder joint. Each intervertebral disk, of which there are twenty-three, is a link in the chain of the vertebral skeleton, giving both flexibility and stability to the whole. In life, movement of one vertebra upon another can only take place as part of a movement of the spine as a whole. Movement may be more marked in one region of the spine, but it can scarcely occur without movement elsewhere. The importance of the disk system in the spine is revealed when we appreciate that altogether the disks comprise one-quarter of its movable length. Pathological disturbances of the mechanics of the spine for the reasons already mentioned rarely involve one disk alone. The individual disks are thicker where mobility is greatest. These regions, the cervical and lumbar respectively, appear particularly prone to certain traumatic lesions.

It is as well that we should refresh our minds upon the nature and structure of an intervertebral disk. It must first be realized that each one is only part of an intervertebral articulation. We are dealing with a synchondrosis associated with two

posterior apophyseal diarthroses which are complementary to it. There is, therefore, a triple joint and not unnaturally we should expect that disturbances of one section of the joint should also involve the others more or less. This is well demonstrated in the profound disturbances of spondylolisthesis, and is probably true in a less marked degree in spondylolysis, fractures of the articular processes, and in arthritic degeneration of the posterior joints. The intervertebral synchondrosis merits the title of universal joint more than any other joint in the body, for it permits all the movements of an enarthrosis (a ball-and-socket joint) with, in addition, the capacity for movement in its vertical axis in response to tension and compression. The focal point, so to speak, around which these movements occur, is the nucleus pulposus embedded in, and maintained in a state of compression by, the cartilaginous annulus fibrosus. The nucleus, which is a semi-fluid structure, has expansile properties when released from its surrounding compression. Mechanically it is said to behave like an incompressible fluid which, with the alterations in shape of the surrounding annulus, helps to distribute pressure more evenly from one vertebra to another. The annulus certainly undergoes significant changes of shape in different movements on the spine, and I think it is useful to think of the nucleus as a resilient ball around which such movements occur.

Each individual intervertebral disk is firmly attached to the vertebra above and the vertebra below through the cartilaginous plate which covers the vertebral surface, the peripheral portion of which is ossified to form the vertebral epiphyseal ring. The annulus is composed of fibro-cartilage. The thin epiphyseal plate is, of course, hyaline cartilage. In the adult it forms a very thin lining covering the exposed cancellous bone of the vertebral surface within the epiphyseal ring, and is the only protection which the cancellous bone has from the variable pressure changes produced within the intervertebral disk—a point of some pathological importance. Other attachments of the disks are provided by the anterior and posterior common ligaments, of which the former are the denser. Under pressure each disk bulges somewhat at its periphery (but it is of interest that uniform pressure of several times *g* does not cause any appreciable diminution of thickness). With changes of movement these bulges vary in amount. The continuous and repeated pressure or tension which they cause upon the peripheral fibrous tissue provokes the characteristic changes of senility; that is, the beak-like ossification from the vertebral bodies or osteo-arthritic spurs seen so readily at the front and side of the disks in skiagrams. The resilience of the intervertebral disks and consequently their flexibility depend, it is said, upon their water content, which diminishes with age. Thus these bulges tend to persist, and yet for the same reason to become smaller. Ossification or calcification around the bulging disks is less likely to occur posteriorly, but it may occur. One should note by comparison the lack of bulging seen in the spines of young patients with ankylosing spondylitis, in which ossification follows the straight line of the peripheral ligaments. As Schmorl has shown, disk bulging may occur also in a vertical direction when there has been a break through the cartilaginous plate referred to previously. In such cases herniation of disk substance occurs into the cancellous vertebral body. A more generalized vertical bulging of intervertebral disk may occur in certain metabolic diseases such as hyperparathyroidism or senile decalcifying spondylitis in which the vertebral bony substance is abnormally soft. The intervertebral disks are relatively avascular structures; they degenerate and become thinner with loss of their characteristic properties when the nutrition of their surrounding tissues is interfered with. This is seen characteristically in tuberculosis, in which the disease starts in the neighbouring bone and produces early degeneration of the disk before it is invaded by tuberculous granulation tissue. Similar disk degeneration may occur as the result of trauma. Absence of the characteristic changes in the vertebral bodies nearby distinguishes the two conditions. Cartilaginous tumours arising from remnants of the notochord are described, but it is probable that many of those described in reports published before 1932 were, in fact, protrusions of disk substance. Although nerve fibres from the spinal nerves are seen to pass on the posterior surfaces of the vertebral bodies, it is probable that the disks are relatively insensitive, and that symptoms produced by pathological changes are due to irritation of surrounding tissues. Particularly is this true posteriorly and laterally (in cases of posterior protrusion) because of the presence of the meningeal structures, the spinal nerve roots, and the spinal nerves. The relation of the latter, of course, accounts for the segmental distribution of symptoms and signs.

We have to consider first the effects produced by the local irritative change, and secondly a profound derangement of all the anatomical structures which go to maintain the stability of the spine, particularly in the region in which the lesion occurs. While, therefore, there may be nerve-root oedema and fibrosis, derangements of the posterior apophyseal elements of the intervertebral joint

complex, tearing of ligamentous attachments, and so on, nevertheless we must recognize the great reflex disturbances in the muscular system which any joint derangement will cause.

Clinical Features

As has been stated previously, lesions of the disks of one sort or another are common. They are often present without giving rise to any symptoms whatsoever. This applies equally to posterior protrusion, which Schmorl has shown to be present in 35 per cent. of all necropsy material studied by him. While these protrusions may not cause any symptoms, those which do have no absolutely clear clinical syndrome. Identical symptoms and signs can be found in other pathological processes, remote from the intervertebral disk, as well as in diseases of the disks without posterior protrusion.

Radiologically there is no characteristic picture. Posterior disk protrusion may be found with a normal skiagram; a skiagram showing disk degeneration does not necessarily indicate that there is mechanical disk pressure upon the neighbouring nerve roots.

In considering the clinical problem, it is useful to apply the simile of an explosive incident. There is a train of events or conditions leading to the setting of the fuse, or the pulling of the trigger, and to the resultant catastrophe. The background of our problem is often a background of physical and psychological defect, incompetent spinal musculature with poor postural control, and an inefficient use of body mechanics in performing the normal tasks. Stressing the lumbar spine by indirect violence while it is in flexion is doubtless one causal factor; there are probably many other inherent defects of the individual which permit the trigger release, namely, the extrusion of disk substance into the spinal canal or into the intervertebral foramen. As a clinical problem, it is difficult to sort out those explosive symptoms and signs which are due purely to the trigger release, and those which are secondary. The kinking or traction of a nerve root and the meningeal coverings causes pain of segmental distribution, paraesthesia, and disturbances of temperature sense. The motor effect will be spasm. The irritative signs are succeeded by those which are paralytic, as neurone damage becomes more complete; analgesia and anaesthesia of segmental distribution are associated with muscular atrophy and contracture, loss of peripheral reflex, and even localized paralysis. The irritative signs are increased by movements of the spine which aggravate the mechanical involvement of the nerve root (such as the flexion of the spine, which automatically occurs when the hip is flexed with the straight knee, or when meningeal tension is accentuated by flexion of the neck), and by all the circumstances which may cause a rise of cerebrospinal fluid pressure, such as coughing or sneezing, straining at stool, or jugular compression. It may be said that much of the explosive effect of such disk lesions is due to the causes I have just enumerated, but in addition there is an overflow of impulses from the affected segment into neighbouring segments, while muscle spasm itself is painful and provokes its own very widespread reflex effects, and, of these, scoliosis is a visible sign. Scoliosis is of a special type, and is best described as a list which transfers body-weight to the opposite limb; less often the list is to the same side (homolateral) and occasionally it alternates almost at will from one side to the other. As I have previously shown elsewhere (Capener, 1933), the one curve is not the mirror image of the other, for in alternating sciatic scoliosis the contralateral curve takes place low down in the spine, whereas the homolateral curve appears to take place at a higher level.

The segmental distribution of pain is not itself sufficient to justify the diagnosis of disk retropulsion, for it is known that stimulation in any part of a spinal nerve segment may produce pain referred throughout the rest of the segment. In experimental work Lewis and Kellgren (1939) have suggested that irritative injections into the supraspinous ligaments may reflexly cause sciatic pain, but recent work of Sinclair and his colleagues (1948) suggests that these effects are the result of direct stimulation of the posterior primary divisions of spinal nerves. The same can be said about many of the other segmental signs. Nevertheless, the persistence of purely segmental signs and symptoms should lead to the serious consideration of the diagnosis of intervertebral disk retropulsion, and this point should, I maintain, add particular emphasis to the form of treatment which I advocate and which as I will show, deals primarily with the widespread effects of such disk disturbances and of other causes of sciatica.

Treatment

In derangements of the knee our programme is one of early support, graduated movements, and re-training. Such a programme is equally necessary in the spine.

The primary treatment should be the application of physiological rest. This does not mean allowing the patient to lie in bed in any position he likes. It does mean control in a physiological position with graduated activity as the pathological process

and clinical signs subside. When the symptoms are of the greatest severity, the spine and lower extremity must be controlled with practically complete immobilization in recumbency. The methods vary from one clinic to another—the use of a plaster jacket with traction upon the affected lower extremity, the use of a plaster spica or even a plaster bed, including the spine and both lower extremities, may be chosen. For most cases, however, the plaster jacket is the most satisfactory. This gives only relative immobilization of the lumbar spine, and does not extend above the nipple line but does come well down on to the pelvis at the back and front. It is applied with slight steadying head traction. It does not support the spine, but it does provide an important aid to the muscular system of the lower spine. After the jacket is applied, rest in recumbency with a knee pillow is ordered for a few days, but is steadily diminished as symptoms subside. Radiant heat and massage for the lower extremity will assist in relieving pain and muscle spasm. Then a graduated course of remedial exercises is started in order to re-train the whole extensor mechanism, including the gluteal muscles, action of which stimulates the spinal muscles synergically. When the acute symptoms have subsided, the patient will still be made to take a considerable mid-day rest in recumbency so as to relieve the readily fatigable spinal muscles. The plaster jacket is retained for from five to twelve weeks according to the severity of the symptoms and the speed with which they subside. In patients with sciatic scoliosis the jacket may require changing, for until spasm is relieved one does not attempt to correct the early deformity. After the necessary period, the jacket is split in the front midline, and can be removed increasingly for the further elaboration of spinal movements. Usually at this time it may be slipped off at night and for baths. Remedial exercises at this stage should include stretching the hamstring muscles. This is not done by forward flexion of the trunk on the hips. The patient carries out straight leg raising in the supine position with a passive support of gradually increasing height, stopping short of pain. For many months afterwards he should be warned not to bend forwards with the knees extended, nor should he sit in bed in a similar position. He must avoid lifting heavy weights from the ground and instead should get "under his weights" by bending the knees.

The course of treatment will extend over a period of three months, and the clinician should by then have been able to decide in most cases whether or not the patient is going to be relieved of his disability without further intervention. The more widespread secondary effects will have subsided, and even the purely segmental signs may have disappeared. The important thing is that in those few cases which do not respond, the neurological signs will have become relatively isolated and clearly defined, and a decision can then be more carefully made as to those cases which can still be treated conservatively, and those which need operation. Always, however, must be borne in mind the fact that occasionally the signs of neurological damage are so complete and paralytic from the outset that operation is almost an emergency.

Results of Treatment

Conservative Treatment.—My associate, Mr. F. C. Durbin (1948), has published the results of an investigation he has carried out into the use of the plaster-jacket treatment for sciatica, in my orthopaedic service at the Princess Elizabeth Orthopaedic Hospital, Exeter, during the years 1936-1945 inclusive. During this ten-year period, 525 patients with sciatic pain were treated. In the investigation there were selected 225 patients who, because of segmental neurological change (such as absent ankle jerk, sensory loss, or muscle wasting) might justifiably be considered to have suffered from intervertebral disk retropulsion. Follow-up was possible in 147 patients of whom there were 82 men and 65 women. Of the cases, 65 per cent. were between the ages of 20 and 40. The plaster-jacket method of treatment was used in 123 patients, and of these 43 were cured, 35 were relieved, and 45 were not relieved, 16 of the last group being subsequently treated by laminectomy. By "cured" is meant complete relief of pain with no recurrence over a period of from two to ten years, the patients continuing in their normal occupations. By "relieved" is meant persistence of very little residual pain, the patient doing heavy duties though often sparing himself the lifting of heavy weights. By "not relieved" is meant that the pain was never completely controlled, or that there were many recurrences requiring rest in bed for more than a few days. Two interesting points showed up: first, that the duration of symptoms before treatment influenced the likelihood of relief. In the failed group, when symptoms had been present for more than a year the figure varied between 41 and 51 per cent. The other point is that loss of ankle jerk, and hypo-aesthesia both tend to persist. On the other hand, simple diminution of an ankle jerk often disappears when symptoms are relieved.

I do not think Mr. Durbin would object if I said that he approached the problem with scepticism in 1946. Allowing for this and the fact that this work

and the after-treatment was, for six of those years, carried out under the very difficult conditions of wartime, the results are of considerable interest. Few figures have been published dealing with the results of the conservative treatment of sciatica; at the same time these figures cannot be considered as final, for there are many variable factors. An illustration of what is being done at Exeter along these lines is given in the Table.

TABLE

PLASTER JACKETS APPLIED IN THE TREATMENT OF SCIATIC PAIN*

(At the Princess Elizabeth Orthopaedic Hospital, Exeter)

1942	54
1943	68
1944	132
1945	154
1946	162
1947	178

* During the first six months of 1948 the number of treatments by plaster jacket is still rising, for 132 have been applied.

Operative Treatment.—An enormous amount of experience has been gained by both neurosurgeons and orthopaedic surgeons in the United States of America. It is interesting to note the changing point of view. That simple removal of protruded intervertebral disk substance is by itself not giving entirely satisfactory results is indicated by the increasing number of combined operations, including lumbo-sacral fusion, which are being reported. A disturbing report is contained in the paper by Aitken and Bradford (1947), in which the experience of one insurance company is reported and 170 cases operated upon between 1940 and 1944 are reviewed. These were all compensation cases, and that this fact influenced the end-result is not denied. Nevertheless, as the authors state, the period in question was one of intense industrial activity because of the war, with every encouragement for patients to work even with a partial disability. The operations were not carried out in a single institution, but were the work of many hospitals and surgeons. Only 13 per cent. were symptom-free and capable of performing heavy laborious work after the operation. Only 17 per cent. were in the group that we would call relieved; 25 per cent. had pain and were only able to do light work; 42 per cent. were classed as bad results; and there was a 3 per cent. mortality rate. Placing the first and second groups together as good results, the comparison of 30 per cent. good and 42 per cent. failures is indeed striking. Two additional points in this analysis are of interest, namely, that the percentage of error in diagnosis, with present diagnostic criteria, was about 40 per cent., and that secondary operations were required in 24 per cent. of all cases.

Conclusions

There are many lesions of the intervertebral disk besides posterior protrusion. There are no unmistakable signs, clinically or radiologically, of disk protrusion. The most suggestive signs of this condition are also given by other pathological lesions of the vertebral column and spinal cord. In the analysis of the clinical state and in planning treatment, one must consider three elements: first, the patient as a whole; secondly, the immediate local lesion; and thirdly, the widespread physiological disintegration. While we all probably recognize in various degrees the need to treat the patient, there is a common failure to treat adequately the explosive effects produced by such spinal derangements. In advocating the use of the plaster jacket for applying rest, one should emphasize the importance of such treatment early, not only because it is the best method of treating all three elements of the problem, but also because it enables us to separate that group of individuals who have a more severe organic lesion likely to require operative intervention, which in any case should be less often needed if this treatment and its after-care are diligently pursued.

I have thought it of value to quote some figures from an investigation of a considerable series in which conservative treatment has been given. At the Princess Elizabeth Orthopaedic Hospital, we have had a relatively large experience. As Geoffrey Jefferson has said to me: "Experience may merely be the repetition of the same error." I hope this is not so in the present example. At any rate it would be relatively harmless.

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Signification Clinique et Traitement des Lésions du Disque Intervertébral

RÉSUMÉ ET CONCLUSIONS

Cette article concernant le "Problème du Disque" constitue un complément à l'étude anatomique et mécanique de la région lombo-sacrée, publiée dans les *Ann. Rheum. Dis.*, 1944, **4**, 29. La théorie est que, quelle que soit l'importance du rôle de la rétropulsion d'un disque intervertébral dans la sciatique, elle est néanmoins accompagnée par un nombre important de manifestations qui doivent être soumises à un traitement prolongé avant que l'on soit en droit de procéder à une intervention chirurgicale.

TREATMENT OF SO-CALLED PALINDROMIC RHEUMATISM WITH GOLD COMPOUNDS

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A relatively rare form of arthritis was described by Hench and Rosenberg in 1941 and in 1944. The syndrome is characterized by frequently recurring attacks of pain, swelling, redness, and disability involving usually one joint at a time, but sometimes multiple joints. The attacks last for short periods and then subside completely without leaving joint residue. They considered it to be a " new disease ", an entity separate from rheumatoid arthritis and distinguishable clinically from other forms of recurring acute arthritis. To this syndrome the name " palindromic rheumatism " was applied.

From an analysis of their thirty-four cases, Hench and Rosenberg outlined the clinical characteristics of palindromic rheumatism. In summary, these were as follows: (1) multiple afebrile attacks of acute arthritis characterized by pain, swelling, tenderness, varying degrees of redness, and increased local heat; (2) frequent recurrences (88 per cent. of cases averaging twenty-three attacks per year) at irregular intervals (few hours to two weeks in most cases); (3) attacks of short duration (80 per cent. lasting a few hours to three days); (4) attacks usually affecting a single joint (90 per cent. of cases); (5) disability often considerable with temporary loss of function of the involved part; (6) complete restitution of joint appearance and function following attacks; (7) para-arthritis, consisting of red tender swellings near a joint (30 per cent. of cases), and frequent involvement of finger pads; (8) absence of general constitutional signs and symptoms; (9) absence of chronic arthritis even when the disease has persisted for years; (10) intracutaneous or subcutaneous nodules (9 per cent. of cases); (11) essentially normal laboratory tests including erythrocyte sedimentation rates, blood uric acid determinations, and radiographs of involved joints; (12) adults of either sex affected equally. Joint biopsies were accomplished in three instances (two during acute attacks and one after recovery); these disclosed subacute cellular reactions in the synovial membrane during attacks, but the cellular condition returned to normal on recovery. Findings frequently described as characteristic of rheumatoid arthritis, such as perivascular collections of lymphocytes, pannus formation, and cartilage destruction, were not found. Neither urate deposits nor collections of eosinophils were demonstrated.

Subsequently, twenty-eight cases have been reported by others as examples of palindromic rheumatism (Thompson, 1942; Mazer, 1942; Vaughan, 1943; Ferry, 1943; Paul and Logan, 1944; Grego and Harkins, 1944; Cain, 1944; Wingfield, 1945; Paul and Carr, 1945; Neligan, 1946; Salomon, 1946; Weber, 1946; Hopkins and Richmond, 1947; Scheinberg, 1947). Some of these have conformed to the clinical characteristics as outlined by Hench and Rosenberg; others have not. From the additional reports no new diagnostic data have been proposed and no definite ideas on aetiology have been offered. Chronic fatigue and emotional strain were notable in several cases (Mazer, 1942; Ferry, 1943; Paul and Logan, 1944; Cain, 1944; Neligan, 1946), and in a few these factors appeared to be related temporarily to the onset or exacerbations of symptoms. The transient afebrile episodes of articular and para-articular swellings prompted some (Vaughan, 1943; Weber, 1946) to consider an allergic basis, but no proof has been offered for this supposition.

Already a host of medications, diets, and procedures have been tried therapeutically. These have included: purine-free and low-purine diets, colchicine, cinchophen, allergy diets, epinephrine, ephedrine, benadryl, pyribenzamine, intravenous and oral calcium preparations, histaminase, histamine desensitization, ergotamine tartrate, eradication of foci, febrile reactions with intravenous typhoid vaccine, bacterial vaccines (stock and autogenous), salicylates intravenously, sulphur preparations, and sulphonamides. In general the results from these various forms of treatment have been negative or equivocal. No report has appeared in the literature on the use of gold compounds for palindromic rheumatism.

We have encountered three patients with frequently recurring transient bouts of acute arthritis the clinical features of which conform strictly to the diagnostic criteria of palindromic rheumatism as described by Hench and Rosenberg. Each of these has responded favourably to treatment with soluble gold compounds.

Case Reports

Case 1.—A 42-year-old housewife of Irish descent, was first seen on July 16, 1946, because of recurrent acute episodes of arthritis. She was the mother of three children, was obese, jolly, and except for two attacks of gallstone colic and subsequent cholecystectomy, had always been in robust health.

Without previous history of rheumatic complaints the first musculo-skeletal symptoms were experienced in October 1941, while she was accompanying her husband on a strenuous business trip which entailed travelling, loss of sleep, and social entertaining. Without known injury, about mid-day, the right wrist rather suddenly became tender and painful on motion. By dinner time that evening the joint and dorsum of the hand were exquisitely painful, tender, hot, and slightly reddened. She was forced to cancel a dinner engagement and a hotel physician administered hypodermic medication. On the following day the wrist was less sore and swollen and sufficiently comfortable to allow her to go shopping. By evening of the third day (fifty-four hours) all swelling had disappeared, but, as she recalled, some tenderness may have persisted for another twenty-four hours.

Approximately two months later (December 1941) a second attack occurred, the proximal interphalangeal joint of the right index finger being involved. The articular manifestations and the duration of symptoms were almost identical with the first episode. At the time the patient was under severe emotional stress because her husband, an army reserve officer, was expecting orders for active military service. From December 1941 to July 1946 she continued to have recurrent bouts of transient acute arthritis, the characteristics of each being monotonously similar. The attacks usually came on rather suddenly, starting with an aching in the joint, and within a few hours pain of a bursting type together with swelling, exquisite tenderness, slight redness, and variable amounts of increased local heat developed. Usually the attacks lasted from eighteen to forty-eight hours, but not infrequently tenderness persisted for one or two days longer; a few attacks lasted for only six hours. They recurred at irregular intervals, sometimes two days apart but usually at intervals of one to three weeks. The longest period of freedom was two months, following a cholecystectomy. It was calculated that approximately 350 attacks had been sustained over a period of four years and nine months. Almost all of these had been accompanied by actual joint swelling and slight redness, but in a few attacks only pain and local tenderness were experienced. The attacks came on at any time, and there was no day-time or night-time pattern. Complete restitution of the appearance and function of joints followed each episode, and there were no interval musculo-skeletal symptoms. Between attacks she felt fine, was active socially, and worked hard at home. There had been no general constitutional symptoms, and during the five year period gained 18 lb. in weight.

Approximately 95 per cent. of the episodes had involved joints of the upper extremities. Most frequent sites had been the wrists, elbows, and metacarpo-phalangeal and proximal interphalangeal articulations. The distal interphalangeal joints (except for the thumbs) had been affected rarely. A few attacks had occurred in the knees, ankles, and bunion joints. In approximately 95 per cent. of instances a single joint had been affected; occasionally two, three, or more had been involved. Several times the whole dorsum of the hand had been so swollen and painful that the individual joints involved could not be identified. Para-arthritic swellings, finger-pad involvement, and intracutaneous or subcutaneous nodules had not made their appearance.

Although no definite precipitating factors were recognized by the patient, the initial bouts appeared to have been related to periods of undue emotional strain. No history of allergic manifestations could be elicited, and the attacks apparently were unrelated to the menses.

Physical Examination (July 16, 1946).—Except for obesity (weight 172 lb., height 62 inches) and for slight tenderness on deep palpation in the right upper abdominal quadrant, general physical examination revealed no abnormal findings. Save for slightly increased crepitus of both knees, detailed examination of the musculo-skeletal system revealed no abnormalities.

Laboratory Data.—These were within normal range. The erythrocyte sedimentation rate was 14 mm. in one hour (Westergren). The erythrocyte count was 4,750,000 per c.mm. of blood and the haemoglobin 12·4 g. per 100 c.cm. The total leucocyte count was 9,400 per c.mm., and the differential count revealed 45 per cent. lymphocytes, 8 per cent. monocytes, 44 per cent. neutrophils, and 3 per cent. eosinophils. The filament count was 33 and the non-filament count 11. Whole blood uric acid was reported as 3·4 mg. per 100 c.cm. of blood, and the blood cholesterol was 200 mg. per 100 c.cm. Basal metabolic rates were minus 14 and 16 per cent. Radiographs of the hands and of the sacro-iliac joints were normal.

Interval Course.—From July 16 to Sept. 13, 1946, the patient had seven episodes of acutely painful, swollen joints, three of which were observed by us. One attack in the right ankle was so severe that she had to be transported from the automobile to the office in a wheel chair. Erythrocyte sedimentation rates taken during this interval ranged from 8 to 16 mm. in one hour; one (14 mm. in one hour) was obtained during an acute episode. From Aug. 13 to Sept. 13, benadryl, 50 mg. four times daily, was taken without apparent effect.

Previous Diagnosis and Treatment.—The diagnosis of gout was made by two physicians. Trials on purine-free and purine-low diets had failed to influence the clinical course. Colchicine, taken in small doses daily and in full doses during attacks, did not influence the frequency or duration of the attacks. Cinchophen was not tried. The best symptomatic relief during an attack was obtained with the use of large doses of acetyl-salicylic acid, phenacetin compound with codeine, or both.

Chrysotherapy.—Treatment with gold thioglucose was begun on Sept. 13, 1946. After an initial dose of 25 mg., a schedule of 50 mg. weekly was followed until a total of 1,025 mg. had been administered. Maintenance doses of 50 mg. every three weeks were then instituted and have been continued. Except for a mild transient stomatitis which lasted for nine days, no toxic reactions have been encountered.

Course during Chrysotherapy.—The attacks continued with their usual frequency and severity until a total of 475 mg. of gold thioglucose had been administered. A change in the clinical course then occurred; the bouts became less severe and less intense, and only three episodes were experienced in the subsequent eleven weeks. After a total of 925 mg. had been given the attacks ceased. From Jan. 15, 1947, until June 8, 1948, during which time maintenance doses of gold were continued, only one minor bout of pain and swelling in a joint was experienced.

Case 2.—A 42-year-old white male, was first examined on July 24, 1946, because of "migratory arthritis" of twenty-one months' duration. Except for the ordinary childhood diseases he could recall no medical illnesses during his life. A right herniorrhaphy and a haemorrhoidectomy had been performed in 1940. He was married and had three sons ages 18, 14 and 12 years.

The patient denied having had any musculoskeletal symptoms before October 1944. At that time he was under considerable nervous stress occasioned by business worries and hard work; for ten years he had averaged fourteen hours at his office daily, six days a week. During that month he experienced an episode of acute pain, tenderness, and limitation of motion in the left shoulder which lasted for four days and then disappeared entirely. From that time he continued to have recurrent attacks of swelling, pain, and tenderness in and about various peripheral joints.

The attacks were characterized by sudden onsets of pain, tenderness, swelling, increased local heat, and varying degrees of redness of a joint or soft tissues in the region of a joint. Often these came on abruptly, the swelling reaching its height within a few minutes. At other times the development was more gradual, and the climax was not reached for several hours; when the onset was gradual, immobility of the part would sometimes prevent the occurrence of actual swelling. The duration varied from a few hours to two days, but it was never longer than four days. An involved part or joint had always cleared up completely without leaving functional residue. At the beginning the attacks recurred at intervals of every two or three weeks, but gradually the tempo increased, and by the time of examination he was experiencing three to fifteen attacks each week. About 40 per cent. of the episodes began in the late afternoon, between 3 and 5 o'clock.

The patient estimated that 400 attacks had been sustained during a period of twenty-one months. Almost every peripheral joint in the body, large and small, had been involved at one time or another. Not infrequently the disability was sufficiently marked to necessitate the use of a crutch or to prevent his driving an automobile. Initially the involvement was always monarticular, but for the six months before examination multiple joint involvement was frequent. Para-arthritic swellings (including finger pads) were not infrequent; sometimes they occurred alone and sometimes in conjunction with actual articular involvement. Neither intracutaneous nor subcutaneous nodules had been noted. Despite the frequency of attacks there had been no loss of weight, and between episodes he felt well.

Physical Examination (July 24, 1946).—No abnormal physical findings of significance were noted on examination except those referable to the musculoskeletal system. Twenty-four hours previously an acute attack had occurred in the left metacarpo-phalangeal joints of the second and third digits, and residual swelling and tenderness were noted. An acute episode had begun six hours previously in the right knee, and had reached its climax at about the time of examination; the joint was moderately swollen, exquisitely tender, painful on motion, and considerably warmer than the opposite knee; full weight-bearing could not be tolerated. The remaining peripheral joints were objectively normal, and there were no abnormal findings referable to the neck or back.

Laboratory Data.—Repeated erythrocyte sedimentation rates ranged from 1·5 to 5 mm. in one hour (Westergren). The erythrocyte count was 5,600,000 per c.mm. of blood with 16·6 g. of haemoglobin per 100 c.cm. The total leucocyte count was 9,400 per c.mm., and the differential count revealed 46 per cent. lymphocytes, 4 per cent. monocytes, 46 per cent. neutrophils, and 4 per cent. eosinophils. Kolmer and Kline tests were negative. Whole blood uric acid was 2·4 mg. per 100 c.cm., and the blood sugar was 106 mg. per 100 c.cm. Basal metabolic rates were recorded as minus 12 and minus 16 per cent. Urinalysis was negative. Radiographs of the sacro-iliac joints were normal.

Interval Course.—From July 26 to Aug. 26, 1946, benadryl, 50 mg. five times daily, was tried without benefit. He continued to have episodes recurring every two to five days, and approximately half the time he was unable to go to his office. Two erythrocyte sedimentation rates (Westergren) taken during this interval were 2 mm. and 3 mm. in one hour respectively.

Previous Diagnosis and Treatment.—Previous diagnoses had included gout, allergic arthritis, and rheumatoid arthritis. He had been given various medications, but none had altered the clinical course of the disease. These included intravenous injections of sodium salicylate and sodium iodide, colchicine, neocinchophen, streptococcus vaccine, injections of thiamine hydrochloride and of vitamin B complex, histamine desensitization, and high-potency vitamin D. He was not sure that salicylates were of benefit in controlling the acute episodes; more often he had resorted to codeine.

Chrysotherapy.—Treatment with gold thioglucose was begun on Aug. 26, 1946. After an initial dose of 25 mg., weekly doses of 50 mg. were administered until a total of 1,175 mg. had been given. Maintenance doses of 50 mg. every three weeks were instituted on Feb. 4, 1947, and have been continued. No toxic reactions have been noted. Erythrocyte sedimentation rates have remained within normal range.

Clinical Course during Chrysotherapy.—No improvement occurred until a total of 625 mg. of gold thioglucose had been administered. A notable reduction in the number of attacks was apparent thereafter, the frequency being reduced to approximately one bout every two weeks. After 1,175 mg. of gold thioglucose were administered, the attacks ceased. Subsequently, during a sixteen-month period, he has remained free from symptoms except for four episodes of acute articular pain and swelling (knee

TABLES

CASE SUMMARIES

	Case 1	Case 2	Case 3
Sex and age	F-42	M-42	M-41
Duration of symptoms (months)	57	21	24
Total number of attacks (est.)	350	400	200
Usual frequency of attacks (days)	7-21	1-5	2-7
Minimal interval between attacks (days)	2	½	2
Maximal interval between attacks (days)	60	21	10
Duration of attacks (usual) (hours)	18-48	6-96	8-16
Percentage monarticular (est.)	95	85	98
Complete restitution of function after attacks	—	—	—
Para-arthritis	0	—	—
Cutaneous nodules	0	0	0
General constitutional reaction	0	0	0
Radiographic findings	0	0	0
Erythrocyte sedimentation rate (range in mm./hr.)	8-16	1·5-5	7-9
Other laboratory data	0	0	0

RESULTS OF CHRYSOTHERAPY

	Case 1	Case 2	Case 3
Total dosage at improvement	475	625	375
Total dosage at remission	925	1,175	575
Total attacks before treatment (est.)	350	400	200
Duration of symptoms (months)	57	21	24
Average number of attacks per year before treatment	*73·4*	*228*	*83·3*
Total attacks during remission	1	4	0
Duration of remission (months)	18	16	6
Average number of attacks per year during remission	*0·66*	*3*	*0*
Other musculoskeletal symptoms during remission	0	0	—

once, elbow once, wrist twice). Each of these episodes has followed a day of strenuous physical work in his orchard. It is noteworthy that during a severe emotional crisis occasioned by the accidental killing of one of his sons by another while the boys were playing with a rifle, no acute articular episode was precipitated.

Case 3.—A 41-year-old male of Spanish descent was first seen on Aug. 20, 1947, because of recurrent pain and swelling of various peripheral joints. Neither his family history nor his past personal history was significant. Mastoidectomy had been performed at the age of 8 years, and tonsillectomy at the age of 35. Except for pneumonia as an infant, there had been no other serious medical diseases. He was married and had two children, ages 14 and 7 years.

During childhood he was treated for vague aching in the knees and numbness in the left arm and forearm, but the details were not remembered. No subsequent musculoskeletal symptoms were noted until the onset of the present illness. In July 1945, two years before examination, he began to have transient attacks of pain, swelling, and stiffness in various peripheral joints. These had continued, skipping from joint to joint, until almost every peripheral joint in the body had been involved at one time or another. Attacks had occurred in the wrists, elbows, shoulders, metacarpo-phalangeal joints, proximal interphalangeal joints, ankles, knees, metatarso-phalangeal joints, and temporo-mandibular and sterno-clavicular joints. The end joints of the fingers had never been involved, nor had there been any symptoms referable to the back or neck.

The individual attacks usually began abruptly, the acute phase lasting approximately eight to twelve hours. As a rule some residual tenderness, aching, and stiffness persisted for two or three days. The episodes usually recurred one to two times each week, and the longest interval without an attack was ten days. The function of joints had always returned to normal following an attack. About 60 per cent. of the episodes were vesperal in time of onset, appearing around 3 to 4 o'clock in the afternoon. Practically every attack had been monarticular, and he recalled only four episodes which involved more than one joint. Approximately 10 per cent. of the episodes were accompanied by para-articular swellings. Neither intracutaneous nor subcutaneous nodules had been noticed. There had been no constitutional symptoms, and he considered himself to be in excellent health. He had sustained approximately 200 attacks over a period of two years.

Physical Examination (Aug. 20, 1947).—No abnormalities were disclosed on general physical examination except for a pedunculated papilloma on the uvula and a left indirect incomplete inguinal hernia. Examination of the peripheral joints and of the back was essentially negative except for those findings referable to the left hand. The metacarpo-phalangeal joint of digit three was moderately swollen, tender on deep palpation, and painful on forced flexion and extension. (An attack had commenced in this joint thirty-six hours previously and was now subsiding.) Observation five days later revealed complete disappearance of all objective manifestations referable to the third metacarpo-phalangeal joint of the left hand, but on this day pain, swelling, increased local heat, and slight redness were present in the left ankle, particularly about the external malleolus.

Laboratory Data.—The erythrocyte sedimentation rate (Westergren) was 9 mm. in one hour, and when repeated three days later was 7 mm. in one hour. The erythrocyte count was 5,490,000 per c.mm. of blood, with 15·5 g. of haemoglobin per 100 c.cm. The total leucocyte count was 8,000 per c.mm., and the differential count revealed 44 per cent. lymphocytes, 8 per cent. monocytes, 46 per

cent. neutrophils and 2 per cent. eosinophils. Urinalysis was negative. Kahn and Kolmer tests were negative. Blood uric acid was 3·8 mg. per 100 c.cm. Radiographs of the sacro-iliac joints failed to reveal any abnormalities.

Previous Diagnosis and Treatment.—No definite diagnosis had been made previously. For a period of six months, shortly following the onset, he had received subcutaneous injections of some type of vaccine. He had taken various capsules and tablets, but the exact type of medication received was not known by the patient.

Chrysotherapy.—Because of our experience with two previous cases, chrysotherapy was begun as soon as the diagnosis was established. Administration of gold thioglucose was begun on Aug. 23, 1947, and after an initial dose of 25 mg., a schedule of 50 mg. once weekly was adhered to until a total of 900 mg. had been given. At this time a mild skin rash on the lower legs, in the natal crease, and in both axillae developed. Treatment was interrupted for three weeks, and then the patient was placed on maintenance doses of 50 mg. every three weeks.

Course during Chrysotherapy.—The attacks continued unabated until 375 mg. of gold thioglucose had been administered. During this time the patient kept a detailed record of the attacks, and they recurred at intervals of one to three days. After 375 mg. had been given the attacks became less frequent; only five were experienced during the succeeding two months. Complete cessation of attacks occurred when a total of 575 mg. had been administered. There have been no recurrences since Nov. 21, 1947, a period of more than six months. During this time, however, he has experienced mild transient aching and stiffness in the shoulders. Erythrocyte sedimentation rates have remained normal.

Comment

The improvement which occurred during chrysotherapy was striking in each case. A marked reduction in the frequency and severity of the attacks resulted in two cases, and in the third the attacks ceased. In a strict sense, however, the remissions were not absolute. Case 1 had a single recurrence during an eighteen-month follow-up period; Case 2 had four recurrences in sixteen months; and although Case 3 had no recurrences in six months he experienced mild transient aching and stiffness of the shoulders. During the periods of quiescence or relative quiescence maintenance doses of gold salts were continued. Whether the attacks will return with their former frequency and severity when treatment is discontinued entirely cannot be answered at this time.

Complete remissions of the disease as well as periods of improvement have occurred spontaneously, without treatment, in a number of previously reported cases. Hench and Rosenberg were able to obtain follow-up reports on twenty-seven of their thirty-four cases. Four of these (15 per cent.) had obtained apparent "cures" and were free of attacks for from seven to eleven years; in three, cessation of the attacks occurred spontaneously; in the other recovery was attributed to treatment with calcium gluconate. In twelve cases (44 per cent.) some change for the better, though not notable, had occurred; in five the attacks became shorter and less frequent, in three they were shorter but as frequent as always, and in four they were less frequent but the duration and severity were the same. It is not likely, however, that the marked improvements in our three cases were spontaneous and merely coincidental to treatment. In each instance the disease was of relatively long duration, and the clinical pattern was well established. In each the clinical course was continuous, with only brief spontaneous interruptions in the attacks before treatment, the longest interruption being for two months (Case 1).

The facts that psychogenic factors may enhance the frequency and severity of the attacks, and that relief of emotional tension may result in improvement, have been observed in several cases. In Ferry's case (1943) the attacks appeared to follow periods of emotional strain and were not noted when nervous tension was absent. In the case reported by Paul and Logan (1944) the bouts of pain and swelling in the joints most often followed "nervous or angry" upsets. In two of Hench and Rosenberg's thirty-four cases the attacks seemed to be induced by nervous or physical fatigue. One of their patients "adopted a baby, quit worrying about herself and lost her attacks". Another improved when he "quit the oil business, became a druggist and began to take phenobarbital daily". Mazer's case (1942) had a remission for a period of four months after orthopaedic shoes had been prescribed "under conditions of heightened suggestibility at a medical shrine in another country". Whereas two of our three patients were under emotional and physical strain at the time of their initial symptoms (strenuous travelling and social activities in Case 1, overwork and business worries in Case 2), these factors did not seem to play a role in the subsequent course of the disease. It is not likely that the improvement from injections of gold salts resulted from mental suggestion, because in each instance several hundred milligrammes of the drug were administered before a change in the clinical picture.

The beneficial results from gold salt therapy raise the question as to whether palindromic rheumatism is a separate entity or an atypical form of rheumatoid arthritis. The exact position of palindromic rheumatism is not yet established, and probably will not be established until more cases can be observed for longer periods of time and

until the pathogenesis of rheumatoid arthritis is better understood. Ropes and Bauer (1945) believe that most, if not all, cases of palindromic rheumatism are really cases of atypical rheumatoid arthritis in which the syndrome of multiple recurrent attacks of pain, redness, and swelling is but a manifestation of the initial stage of the disease. In their experience the majority of patients with the "palindromic syndrome" have evidence of rheumatoid arthritis, such as fusion of the sacro-iliac joints or other characteristic radiographic changes, or they finally develop a progressive symmetrical joint disease.

Certainly rheumatoid arthritis may present variable clinical patterns. Not all cases conform to the so-called typical picture of insidious onset, chronic progression (with or without incomplete remissions), and inevitable crippling. Our concept of the disease has been broadened considerably during the past few years, and atypical forms with various types of onsets and clinical courses are being recognized with increasing frequency. Some cases of rheumatoid arthritis begin in a hit-and-miss fashion, with periodic bouts of transient arthritis which clear up completely between attacks and which initially fail to leave joint residues. It may take months or even years for such cases to settle down to a progressive crippling disease. Hench (1947) has recognized this atypical form as "episodic rheumatoid arthritis" and believes that it may be validly differentiated from palindromic rheumatism. He contends that in "episodic rheumatoid arthritis" the attacks tend to recur in favourite sites; para-arthritis is absent or rare, and involvement of finger pads never occurs; the attacks tend to last longer, occasionally weeks; the interval between episodes is often shorter, the attacks sometimes running together; constitutional symptoms and signs are likely to be present.

If "palindromic rheumatism" and "episodic rheumatoid arthritis" are distinct entities, clinical differentiation is of considerable importance. Each has an entirely different prognosis. From the practical standpoint, however, it is often difficult and sometimes impossible to make such differentiation. After taking all differentiating points into consideration the physician frequently ends up with some points for and some against each diagnosis. For example, we now have under observation two patients with transient articular reactions which affect individual joints for such short periods of time as a few hours or a few days. But in each, some finding characteristic of rheumatoid arthritis is also present which prevents a diagnosis of palindromic rheumatism if strict criteria are adhered to. A third case under observation had early features typical of palindromic rheumatism, but thirteen months after the onset developed progressive joint changes characteristic of rheumatoid arthritis. Such experiences suggest to us that palindromic rheumatism probably represents an atypical form of rheumatoid arthritis in which the usual characteristics have not yet become manifest.

If further trials with chrysotherapy in cases of palindromic rheumatism substantiate the favourable results obtained in the three cases reported herein, some weight may be added to the contention that this syndrome represents merely an atypical form of rheumatoid arthritis. However, the results could be interpreted as meaning only that another form of arthritis may respond to gold salt therapy. In addition to rheumatoid arthritis, pleuropneumonia-like arthritis of mice and some cases of psoriatic arthritis are known to be benefited by chrysotherapy.

Summary

Three cases with the typical clinical characteristics of so-called palindromic rheumatism are reported. Each case responded favourably to treatment with soluble gold compounds.

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Aurothérapie du Rhumatisme dit Palindromique

Résumé

Les auteurs décrivent trois observations de malades présentant les caractéristiques cliniques typiques du rhumatisme dit palindromique. Chacun a réagi favorablement au traitement par des sels d'or solubles.

RHEUMATOID ARTHRITIS AND PSORIASIS: STATISTICAL STATEMENTS*

BY

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During the 125 years that have passed since attention was first drawn to a possible linkage between the two disorders of rheumatoid arthritis and psoriasis, this problem has been dealt with in a long series of publications, especially by French, German, and Scandinavian authors. The problem has two aspects, statistical and clinical. Statistically an attempt has been made to find out whether the simultaneous occurrence of rheumatoid arthritis and psoriasis is more than a chance occurrence; clinically, records of cases of simultaneous occurrence of the two disorders are studied to ascertain whether in such cases either or both complaints follow a course different from the usual.

Up to now opinion on these questions has differed widely, and from the results reported it can often be guessed whether the material has originated from dermatological or general medical departments, the different points of view being also reflected in the terminology employed, respectively psoriasis arthropathica and polyarthritis (or polyarthrosis) psoriatica.

The present publication chiefly deals with the statistical aspect of the problem.

Two important recent works on the subject are both from Scandinavia, one by Heinild from Denmark (1942), and one by Romanus from Sweden (1945).

Heinild's Investigation

On a thorough examination of the literature on polyarthritis psoriatica Heinild found that, in 1942, the statistics comprised more than 300 cases. It is generally said that from 1 to 5 per cent. of cases of psoriasis are associated with articular changes, and from 1 to 5 per cent. of cases of chronic polyarthritis seem to be associated with psoriasis. In his own material, comprising 271 patients with chronic polyarthritis, Heinild found psoriasis in 3 per cent. of cases, whereas psoriasis did not occur among 270 patients suffering from different arthroses.

The Investigation of Romanus

On examination of 768 patients with psoriasis Romanus found rheumatoid arthritis in 17 (2·2 per cent.). This is a minimum figure, as Romanus only includes patients who have been hospitalized for their arthropathy; however, on the basis of it Romanus believes he can dismiss the possibility of a linkage between the two disorders because, according to his calculations, the frequency of polyarthritis is not greater in this material than *the calculated total risk* of polyarthritis within the same age groups of the Swedish population as a whole.

The Present Investigation

The reason why opinions about the possible association between these two disorders still differs so widely is first and foremost that no previous publications have included suitable controls. Such material will be produced here.

The two groups of patients to be compared originate from two municipal hospital departments in Copenhagen, namely the Department of Physical Medicine of the Municipal Hospital, and the Medical Department of the Sundby Hospital.* In both departments a special interest was taken in psoriasis and, moreover, the great majority of the patients were observed by the same examiner (Sv. Clemmesen), so that it may be taken for granted that the diagnosis of psoriasis has been established on the same criteria in both groups and that, practically, all cases of psoriasis occurring in the groups have been included in the statement. In addition, the two groups are comparable because the patients originate

* Read before the First European Congress of Rheumatology, Copenhagen, September 1947.

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* I am indebted to Professor H. C. Gram, M.D., for kind permission to use case records from his department.

from the same geographical and social milieu, the sex incidence and the curves representing the age incidence being very nearly identical.

The following results have been arrived at. When 10,000 case records with consecutive numbers for the years 1934 to 1938 from the medical department of the Sundby Hospital were studied, the diagnosis of psoriasis was found 43 times (4·3 per thousand), and examination of the records of 1,000 patients treated for chronic polyarthritis in the department of physical medicine of the Municipal Hospital in the course of the years 1941 to 1947 disclosed 31 patients, or 3·1 per cent., with psoriasis. The frequency of psoriasis among patients with rheumatoid arthritis is thus seven times that among patients with general medical disorders.

Now, as is known, both the disorders in question are rife, so that a "chance" coincidence must inevitably occur now and again, but such a preponderance as has been ascertained in this material can be explained only by certain aetiological or pathogenetic factors being common to the two diseases.

As it can thus be considered statistically proved that there is a linkage between the two disorders, we have to leave it to clinical research to find out whether polyarthritis psoriatica constitutes a special clinical entity, in the sense that its course, and thus its prognosis and treatment, differ from those of other forms of chronic polyarthritis.

The simultaneous fluctuations in the affection of the skin and in the arthropathy have been pointed out. However, it is only in a minority of cases that such a parallelism can be shown, and this is true of asymmetrical occurrence, involvement of the terminal joints of fingers and toes (Hench, 1936; Fletcher, 1947), and of a particularly mutilating form which, however, may also occur without simultaneous occurrence of psoriasis (Comroe, 1944).

In a detailed analysis of seventeen of his own cases, Heinild found that the disorder by no means differs from "cases of polyarthritis of common occurrence."

It is just possible that some of the discrepancies may be due to the polyarthritis-psoriatica-group perhaps not being homogeneous, since, as mentioned, some cases may occur as the result of a chance coincidence of the two disorders (and, consequently, cannot be expected to manifest themselves differently from other cases of polyarthritis), whilst other cases must be termed "genuine", expressing the common causal factors of the disorder of the skin and of the arthropathy.

The modern serological technique with antistreptolysin titre, agglutination reaction for haemolytic streptococci, etc., will perhaps prove helpful in elucidating the problem. While the agglutination reaction is stated to be positive in from 60 (*Year Book of General Medicine*, 1946) to nearly 80 (Kalbak, 1947) per cent. of cases of rheumatoid arthritis, four out of my eight patients with polyarthritis psoriatica last observed had a negative reaction, two of the four positive reactions being very faint (1/80).

My cases of polyarthritis psoriatica comprised twenty-one women and ten men. In twenty-nine cases the arthropathy was classified as chronic primary (or psoriatic) polyarthritis, in one case as secondary chronic polyarthritis (after rheumatic fever), and in one case as chronic gouty polyarthritis.

No cases of polyarthritis occurred among the forty-three medical patients with psoriasis, but three of the patients had arthroses of the knees, two had gonorrhoeal arthritis, and one had gouty arthritis.

Summary

In 10,000 medical patients psoriasis of the skin was found in 4·3 per thousand, while amongst 1,000 patients suffering from rheumatoid arthritis psoriasis was found in 3·1 per cent.

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La Polyarthrite Chronique Progressive et Psoriasis de la Peau; Considerations Statistiques

RÉSUMÉ

En 10,000 malades médicals psoriasis de la peau a été trouvé en 4·3 pour mille, tandis qu'en 1,000 malades souffrants d'arthropaties infectieuses psoriasis a été trouvé en 3·1 pour cent.

RHEUMATOLOGICAL HAND AND FINGER SYMPTOMS

BY

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Rheumatological symptoms in hands and fingers occur frequently and are very important in practice, but they have not received the attention in the literature which their significance deserves.

Various Hand and Finger Symptoms

The Usual Rheumatoid Arthritic Changes.—The hand symptoms occurring in ordinary rheumatoid arthritis are typical and well known: swelling of the joints, muscular atrophy, ulnar deviations, subluxations, trophic disorders, etc. A characteristic feature is the symmetric spread of the joint changes.

Atypical Arthritic Changes.—An " atypical " form of rheumatoid arthritis has been described by this author (1946). It is characterized by the joint symptoms being asymmetrical. Muscular atrophy and consequent ulnar deviation do not occur to any great extent, nor do " trophic " skin symptoms. From the practical point of view it is important that there is little progressive tendency in these cases. The risk of invalidism is therefore smaller than with the common type of rheumatoid arthritis, despite the fact that the joint changes may be quite pronounced, so that large exudates and destructive changes are present in the interphalangeal joints. The sedimentation rate usually remains low for long periods, with the joint symptoms restricted to hands and feet. Nevertheless, in a few cases exacerbations and progress may be observed.

Osteoarthropathia Mutilans.—This is a strange phenomenon that may arise with rheumatoid arthritis, as well as in psoriatic arthropathy and in certain organic nerve diseases. It is characterized by particularly extensive destructive changes in the bone, so that the epiphyses and large parts of the diaphyses disappear. The remaining fragments of bone have usually a characteristic form with tapering pointed ends.

Osteo-arthropathia mutilans was described in 1913 by Pierre Marie and Léri in connexion with rheumatoid arthritis. Destructive changes in the bone cause shortening of the finger skeleton in relation to the skin and the soft parts; the result is that these crease like the segments in binoculars. Pierre Marie and Léri for this reason introduced the name of "*main-en-lorgnette*".

Pathologically Pierre Marie and Léri discovered fatty degeneration in bone marrow and soft parts, hyperaemia of the subcutaneous tissues, and a granulation tissue rich in vessels between the ends of the bones. There have since been descriptions of a number of cases. Other joints besides the fingers may also be affected. The author published two cases of this type in 1938 and has since had the opportunity to observe some twenty more. In two cases it was possible (1947) to undertake histological investigations (Dr. F. Wahlgren, Head of the Pathological Department, Södersjuk-huset). The most striking feature was the high degree of bone atrophy. The spongy tissue with its trabecula was almost entirely gone, and the inside of the bone was filled with fat marrow. Even the cortex was highly atrophic and was represented only by a shell as thin as paper.

Psoriasis.—The connexion between psoriasis and rheumatoid arthritis is not quite clear. Some consider that the occurrence of rheumatoid arthritic symptoms with psoriasis is only an accidental coincidence of two common affections. Others assume that there is a causal connexion and that therefore a real psoriatic arthropathy exists, which attacks hands and feet particularly and especially the distal interphalangeal joint. Changes in the nails are common, and mutilating changes are seen now and then in such cases.

Finger Oedema.—This may be present in inflammatory conditions in the hands in rheumatoid arthritis, and also in climacteric arthritis and, according to Kahlmeter (1936), it may be associated with stiff shoulders. Finger oedema is seen also, together with changes in the palmar aponeurosis, in the Ask-Upmark (1944) arm-hand-finger syndrome in cardiac affections.

Heberden's Nodes.—These, of course, do not usually give trouble, but occasionally pain may be present. This is often relatively insignificant and

transitory. Occasionally the Heberden nodes perforate and a thick jelly-like mass is evacuated. This phenomenon has been described by Gross (1937), under the name of "degenerative myxomatous cysts of the synovia". Surgical treatment does not appear to be indicated. In the cases the author has had occasion to observe, the perforation opening closed up spontaneously.

Bouchard's Nodes.—These are of the same nature and about of the same size and appearance as the Heberden nodes, but are located on the proximal interphalangeal joints. Both Bouchard and Heberden nodes are more common in women than in men, and likewise osteo-arthritis in the carpo-metacarpal and the metacarpo-phalangeal joints of the thumb; but the tendency is for osteo-arthritis in the other joints of the fingers to occur mostly in men.

Knuckle Pads (Garrod, 1893).—These consist of protuberances about half the size of a pea on the dorsal aspect of the proximal interphalangeal joints. They are of firm consistency and move freely over the joint, which is not affected, but they adhere to the skin and there may be slight pain and a feeling of tension when the finger is bent. In the author's opinion excision may sometimes be indicated, but it does not always ensure freedom from trouble. If subjective signs are present the cases are most often wrongly diagnosed as rheumatoid arthritis. The differential diagnosis is not made easier for the inexperienced by the fact that rheumatic nodes of the same macroscopic appearance and with the same localization may be present in rheumatoid arthritis.

Since Garrod's publication, knuckle pads have also been described by Parkes Weber (1938), Wessling (1937), Kranz (1938), and others. Many of Garrod's cases had Dupuytren's contracture, and in some of them this affection occurred in the family. Two of the author's cases displayed changes that entirely agree with those in Dupuytren's contracture (Dr. F. Wahlgren). In others a fibroma-like histological picture was present. According to Lund (1941), Dupuytren's contractures and knuckle pads are often encountered in epileptics. The designation "helodermia" employed by many authors is incorrect, according to Kranz (1938), as this indicates another affection.

Hyperkeratoses.—The hyperkeratoses on the basal interphalangeal joints are of quite another nature from knuckle pads. They may be massive, and they are possibly identical with the changes described by Moncorps (1936-37) under the name of "keratosis supracapitularis pulvinata".

Tendinitis Nodosa.—Tendinitis nodosa in the fingers occurs, of course, as an isolated phenomenon, but nodular tendinitis is also common in rheumatoid arthritis. Quervain's tendinitis, tendovaginitis stenosans, is a constriction of the radial tendon sheath under the dorsal carpal ligament and gives rise to characteristic symptoms.

Arthralgia in the fingers and joints of the hands is often met with, especially in younger women (Jonsson, 1946a). For the reason that rheumatoid arthritis may start with similar symptoms, the differential diagnosis is not always easy. Consequently such cases are often wrongly diagnosed. The same is the case with myalgia in the hand musculature.

Congenital Anomalies.—Congenital hand and finger anomalies do not generally present much of rheumatological interest. An exception is constituted by "hammer fingers", an anomaly consisting in the fifth finger on both hands being acutely flexed at the basal interphalangeal joint and hyperextended at the metacarpo-phalangeal joint. These cases are often diagnosed as rheumatoid arthritis.

Summary

Rheumatological hand and finger symptoms are common and important in practice.

The hand symptoms in ordinary rheumatoid arthritis are well known. An atypical form of rheumatoid arthritis is described by the author, and its characteristics include asymmetrical joint symptoms and absence of atrophic symptoms. The joint changes may be quite pronounced, but are usually restricted to hands and feet; the tendency to progression is slight.

Reference is made to osteoarthropathia mutilans. The author has had an opportunity to investigate two cases histologically. The most striking feature was the high degree of bone atrophy.

Finger oedema, Heberden and Bouchard nodes, and knuckle pads (Garrod) are mentioned. The connexion between knuckle pads and Dupuytren's contracture described by Garrod is illustrated by the author, who in two cases of knuckle pads found histological changes similar to those in Dupuytren's contracture.

Brief mention is made of a number of other hand and finger symptoms of rheumatological interest, including arthralgia of the fingers and joints of the hands (author). Such cases are often wrongly diagnosed as rheumatoid arthritis and have, therefore, a practical importance.

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Manifestations Rhumatismales au Niveau de la Main et des Doigts

RÉSUMÉ

Dans la pratique les manifestations rhumatismales au niveau de la main et des doigts sont communes et importantes.

L'atteinte de la main est bien connue dans l'arthrite rhumatismale. L'auteur décrit une forme atypique d'arthrite rhumatismale, dont les caractéristiques comprennent des manifestations articulaires asymétriques et l'absence de troubles trophiques. Les modifications articulaires peuvent être très marquées, mais sont généralement limitées aux mains et aux pieds, avec faible tendance progressive.

L'auteur mentionne les oedèmes des doigts, les nodules d'Heberden et de Bouchard, et les nodosités articulaires (Garrod). Le rapport entre les nodosités articulaires et la contracture de Dupuytren décrite par Garrod est illustrée par l'auteur qui a trouvé, dans deux cas de ces nodosités, des lésions histologiques semblables à celles qui sont décrites dans la contracture de Dupuytren.

L'auteur mentionne brièvement un certain nombre de manifestations rhumatismales au niveau de la main et des doigts présentant un intérêt au point de vue rhumatologique, notamment l'arthralgie des doigts et des articulations de la main. Ces manifestations sont souvent et à tort considérées comme des cas d'arthrite rhumatismale et ont donc une importance pratique.

INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES

More than 150 physicians from foreign countries are expected at the International Congress on Rheumatic Diseases to be held at the Waldorf Astoria in New York City from May 30 to June 3, 1949. Many of these physicians will present papers before the plenary sessions which will be held in the mornings. In the afternoons clinics will be held at several of the New York hospitals.

Papers to be read before the Congress will include, in addition to presentations by prominent U.S. authorities, many by distinguished foreign guests, among them being Lord Horder (London), Jacques Forestier (Aix-les-Bains, France), Eric Jonsson (Stockholm), Imre Barsi-Basch (Budapest), Prof. S. de Seze (Paris), Svend Clemmesen (Copenhagen), William Tegner (London), Henrik Seyfarth (Oslo), P. Barcelo (Barcelona), Veikko Laine (Heinolan, Finland), and Fernando H. Ramos (Montevideo).

The official languages of the Congress will be English, French, and Spanish, but instantaneous translations of the scientific papers given at the plenary sessions will be made by means of the I.B.M. wireless system. The meeting is open, and the registration fee is $10.00.

ABSTRACTS

[This section of the ANNALS *is published in collaboration with the two abstracting Journals,* Abstracts of World Medicine, *and* Abstracts of World Surgery Obstetrics and Gynaecology, *published by the British Medical Association. The abstracts are divided into the following sections: acute rheumatism; chronic articular rheumatism (rheumatoid arthritis, osteo-arthritis, spondylitis, miscellaneous); sciatica; gout; non-articular rheumatism; general pathological articles; other general articles.. At the end is a list of articles that have been noted but not abstracted. Not all sections may be represented in any one issue.]*

Acute Rheumatism

The Familial Incidence of Rheumatic Fever. I. A Discussion of the Relationship Between a Positive Family History and the Development of Rheumatic Fever in Individuals of Military Age. II. A Statistical Study of the Familial and Personal History of Rheumatic Fever. GRIFFITH, G. C., MOORE, F. J., MCGINN, S., and COSBY, R. S. (1948). *Amer. Heart J.*, **35**, 438.

Over 3,000 patients with rheumatic fever and 3 control groups (1,397 people) were studied. The authors found that the occurrence of rheumatic fever in the family increases the risk of the individual developing the disease while he is still in contact with his family, but not after he is separated from it. There does not, therefore, appear to be a strong and inherited susceptibility. The occurrence of multiple cases in families could be explained either on the basis of common environment or contagion. The authors regard the data as indicating the dominant role of contagion in the development of rheumatic fever. *R. T. Grant.*

Epidemiologic Study of Seven Hundred and Fifty-seven Cases of Rheumatic Fever. QUINN, R. W. (1947). *Arch. intern. Med.*, **80**, 709.

In the United States Navy the incidence of rheumatic fever rose from 0·73 per 1,000 in 1940 to 2·29 in 1944, when the disease was second only to simple fractures in causing loss of manpower. The increase coincided with epidemics of haemolytic streptococcal infection; 21·5% of the men already had valvular heart disease at the time of discharge.

This paper deals with 757 patients of 1,470 admitted to a naval rheumatic fever hospital during 1945-6. At least 25% came from towns, and 24·5% had had a previous attack of rheumatic fever; 54·4% first contracted the disease at the age of 17 to 19 years, and 77·4% during their first year of naval service. The heaviest incidence was in December and January; 72% had a history of previous respiratory infection. Prophylactic sulphonamides caused a dramatic but temporary fall in incidence, sulphonamide-resistant strains soon appearing. In training centres the quarters were crowded and frequently ill-ventilated, especially in winter, and susceptible recruits were constantly arriving. In ships the accommodation, though crowded, was usually well-ventilated and streptococcal infections were uncommon.

Acute Rheumatism in Pregnancy. MCKEOWN, F. (1948). *J. Obstet. Gynaec. Brit. Emp.*, **55**, 50.

Two cases of pregnancy complicated by acute rheumatic heart disease are described. In neither case was there clinical evidence of heart disease before delivery. One patient died 2 hours after delivery with symptoms of shock, and the other developed acute abdominal pain 9 hours after delivery and died in a few minutes. In both cases necropsy and histological examination revealed recent rheumatic carditis and valvulitis.

Six cases of mitral stenosis in pregnancy in which the patients died from cardiac failure were examined for evidence of recent rheumatic carditis. In 4 there were signs of recent disease, and 1 had subacute bacterial endocarditis. In the sixth there was established mitral stenosis, but no evidence of recent rheumatic carditis.

It is suggested that in all cases in which the patient dies from obstetric shock without obvious cause the heart should be examined histologically for evidence of rheumatic carditis. *L. W. Lauste.*

The Determination of the Prognosis of Pregnancy in Rheumatic Heart Disease. BUNIM, J. J., and RUBRICIUS, J. (1948). *Amer. Heart J.*, **35**, 282.

Observations were made through pregnancy and the puerperium on 142 women with rheumatic heart disease; it is concluded that pregnancy itself has little effect on the prognosis in rheumatic heart disease.

The Relationship Between Rheumatic Carditis and Subacute Bacterial Endocarditis. MACILWAINE, Y. (1947). *J. Path. Bact.*, **59**, 557.

Aschoff bodies in the myocardium of patients with infective endocarditis have been noted in many reports in the literature. The author reviews the evidence on their significance, and concludes that they do not represent a reaction to the bacterial infection, but that their presence is evidence of a rheumatic carditis. In the work here recorded, 34 cases of subacute, and 12 cases of acute, bacterial endocarditis were studied histologically. The author concludes that in the majority of cases of subacute, and in a smaller percentage of cases of acute, bacterial endocarditis the bacterial lesion is superimposed upon the site of an active rheumatic carditis.

[The argument of course breaks down if the lesions observed are not specific reactions to the rheumatic infection.] *Kenneth Stone.*

The Treatment of Rheumatic Polyarthritis with Acid Azo Compounds. SVARTZ, N. (1948). *Rheumatism*, **4**, 180.

The author considered salicylazo-sulphapyridine, which she abbreviates to " salazopyrin ", to be worthy of trial in the treatment of polyarthritis. On oral administration much of this drug was not broken down but was excreted unchanged in the urine. It was found by histological experiment that this compound had an affinity for connective tissue, where it formed " depots " before being broken down locally into amino-salicylic acid and sulphapyridine.

The dose was 6 g. in 24 hours, which was reduced as improvement occurred. Of 107 patients with rheumatic fever who were given this drug and could be followed up adequately, 95 " have fully recovered or have only slight symptoms ". The author regards these results as encouraging and gives a temperature chart and case histories of patients suffering from acute polyarthritis who were treated with salazopyrin. On 475 patients suffering from chronic polyarthritis and treated with the compound, 307 were followed up; 63% recovered or showed improvement. She considers that more would have responded favourably if they had been more persevering in taking the compound, but many patients found that the treatment was expensive or produced toxic symptoms and so they discontinued it. Several patients who complained of toxic manifestations with fever and rash could be desensitized by the administration of much smaller doses. Periarticular injections were also tried with " undoubted effect ". A case is described of a patient with ankylosing spondylitis who responded well to the treatment.

[Apparently the author considers rheumatic fever and rheumatoid arthritis as manifestations of the same disease. The results of therapy do not differ from those ascribed to the infinite number of therapeutic procedures already advocated for these conditions.] *W. Tegner.*

Observations on the Efficacy of Benadryl in the Therapy of Rheumatic Fever. UNITED STATES NAVAL MEDICAL RESEARCH UNIT NO. 4 (1948). *Nav. med. Bull., Wash.*, **48**, 380.

" Benadryl ", in increasing dosage up to 500 mg. per day, was administered over a 21-day period to 8 of 16 patients exhibiting clinical or laboratory abnormalities attributed to long-continued activity of rheumatic fever. No apparent alteration in the course of the patients either during or after benadryl therapy was observed. An unpleasant reaction, manifested by facial erythema, throbbing frontal headache, anorexia, nausea, and vomiting occurred upon cessation of benadryl. The failure of benadryl favourably to affect the course of chronically active rheumatic fever is to be expected. A review of the pharmacology of benadryl and the recent report of its effectiveness in the prevention of anaphylactic vascular lesions in experimental animals suggest its trial in the prophylaxis and treatment of early acute rheumatic fever at a station where suitable clinical material is available.—[Summary and conclusions.]

Nodules in Acute Rheumatism. (Maladie de Bouillaud. Les nodules de Meynet.) LUTEMBACHER, R. (1948). *Ann. Med.*, **49**, 310.

This paper describes the cutaneous nodule of acute rheumatic disease under the briefer but parochial term of Meynet's nodule. This is contrasted with the syphilitic plasmoma of Unna and the follicle of Koester [again the author's terminology]. Histological appearances of two nodules from one case are described, but no technical data are given with the photomicrographs (fixation, staining method, magnification), and there are no references to the literature. He likens one stage of the nodule under discussion to the Aschoff nodule of the heart, but this is not as helpful as it might have been since he gives no evidence of knowing the two very different focal lesions which occur in the heart in acute rheumatic disease. Inoculation with material from one of the nodules is said to have produced torticollis and myositis in a rabbit. *A. C. Lendrum.*

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Results of Surgical and Orthopaedic Treatment of Stiffness of the Knee in Flexion in 70 Cases of Chronic Progressive Polyarthritis. (Résultats du traitement chirurgical et orthopédique des raideurs du genou en flexion dans 70 cas de polyarthrite chronique évolutive.) FORESTIER, J., and HERBERT, J. J. (1948). *Sem. Hôp. Paris*, **24**, 600.

The authors describe their methods of dealing with flexion-contracture of the knee in cases of severe rheumatoid arthritis.

Rheumatoid Arthritis in Children. A Clinical Study. PICKARD, N. S. (1947). *Arch. intern. Med.*, **80**, 771.

A study was made of 35 cases of rheumatoid arthritis in children, 10 being under the author's own observation.

Precipitating factors were infection, trauma, and allergy. Culture of joint fluids failed to yield pathogenic organisms, and cultures from the nose and throat did not differ from those of controls. Respiratory infection preceded the onset of arthritis by 3 to 10 weeks in 16 cases. There had been trauma in 10 cases and allergic symptoms in 2. Of 28 cases studied for 5 years or more, 9 relapsed after periods of up to 8 years and 2 after puberty. Relapses tended to be more damaging to the joints than did the original attack. Pathological changes in the synovial membrane in children resembled those in adults, but pannus formation was more limited and cartilage destruction less. In no case were the spinal or sacro-iliac joints involved, though one relapse took the form of ankylosing spondylitis. The bones showed calcium deficiency and this persisted even after complete quiescence. Two patients in this series developed cardiac disease. In 1 case amyloid disease was the cause of death, this complication being more common than is generally recognized. Enlargement of the liver and spleen occurred in 6 and 5 cases respectively, but general enlargement of the lymph nodes in only 1.

Gold therapy is regarded as disappointing. Of the 35 patients, 3 died and 14 recovered completely, the rest being crippled. In spite of the danger of relapse the author holds that this 40% recovery rate justifies a more hopeful prognosis than is usually given. *H. F. Turney.*

Gold Therapy of Rheumatoid Arthritis in Children. (Kronisk polyartrit hos barn och dess guldbehandling.) BILLE, S. V. (1948). *Nord. Med.*, **37**, 307.

The author gives a brief account of the 65 children under 15 treated for all forms of chronic polyarthritis between 1934 and 1946. Two-thirds of them were treated with gold; reports of the use of gold in children are few. The total amount per course varied from 100 to 400 mg. for a weight of 15 kg. to 800 to 1,000 mg. for a weight of 50 kg. It was given in 10 injections, usually intramuscularly. There were reactions in 84%, such as an increase in pain or fever, and 17% developed albuminuria or haematuria, a higher percentage than is usual in adults; 53% developed definite complications, mainly affecting the skin (40%) or the blood (12%). There was no case of agranulocytosis, encephalitis, or serious purpura. The incidence of complications was unrelated either to the number of injections or to the total amount given. The results as assessed at the last discharge showed improvement in 84%, and very considerable improvement in 58%. *A. M. M. Wilson.*

Complications of Gold Treatment of Chronic Polyarthritis. (Komplikationer vid guldbehandling av kroniska polyarthriter vid Åsö och Södersjukhuset.) NYSTRÖM, G. (1948). *Nord. Med.*, **37**, 499.

The author reports his experiences with 762 courses of gold given to 620 patients suffering from chronic polyarthritis. Of the patients 62% were women; 56% of them and 66% of the men were under 50; the majority had had the disease for under 5 years. Three-quarters of the courses were of "solganal" and the total gold given varied from 0·8 to 1·0 g. The author agrees with Sundelin that reactions, hypersensitivity, and complications are difficult to differentiate, but gives the following figures. Reactions and complications occurred in 40%, leading to cessation of treatment in 6·8% and death in 2 cases. Reactions (which led in no case to cessation of treatment) affected mainly the blood—the leucocyte count fell temporarily to below 3,000 in 9%, eosinophilia of over 15% occurred in 2·5%, and the platelet count fell to below 150,000 in 18%. Haemoglobin values and red cell counts also often fell. Albuminuria occurred in 1·6% and haematuria in 0·5%. Complications (for which treatment had to be stopped) affected mainly the skin (4·4%), but there were no serious cases of dermatitis. Encephalitis and panmyelophthisis accounted for the fatal cases. *A. M. M. Wilson.*

Gold Treatment in Rheumatoid Arthritis. (Guldbehandling vid kronisk polyartrit.) SUNDELIN, F. (1948). *Nord. Med.*, **37**, 303.

The author reports the results of treating 1,904 cases of rheumatoid arthritis with 2,817 courses of gold injections between 1941 and 1946. The immediate results were good; in over 90% there was subjective and objective evidence of general and local improvement. Later results were variable and have not been fully worked out. Minor complications occurred in 50% and severe ones requiring cessation of gold treatment in 4·5% (severe dermatitis, granulopenia, purpura, encephalitis, and pneumonia). There were 7 deaths, all in women, an incidence of 0·36%. The author gives his views on gold therapy.

Tests of Possible Antagonism of Gold for Histamine Toxicity and Certain Allergic Reactions. KUZELL, W. C., and DREISBACH, R. H. (1948). *Proc. Soc. exp. Biol. N.Y.*, **67**, 157.

In view of the favourable claims for an allergic factor in rheumatoid arthritis and because gold salts seem to alter favourably the course of the disease, it was thought desirable to determine whether gold could prevent histamine toxicity and anaphylactic shock and could beneficially effect the Arthus phenomenon in animals. Various experiments carried out on guinea-pigs indicated that gold had no such action, and it was concluded that the therapeutic action of gold did not rest on inhibition or suppression of allergic responses.
David P. Nicholson.

Production of Experimental Polyarthritis by Pleuropneumonia-like (L4) organisms in Rats and Preliminary Results on Protective Effects of a Gold Product. TRIPI, H. B., and KUZELL, W. C. (1947). *Stanford med. Bull.*, **5**, 98.

A polyarthritis, somewhat similar clinically and pathologically to human rheumatoid arthritis, may be produced in mice, cattle, sheep, rats, and goats, by the intravenous or peritoneal injection of strains of pleuropneumonia-like organisms. This experimental arthritis responds to gold salts.

These organisms may be obtained from men and women suffering from gonorrhoea, and from women with non-specific cervicitis and trichomonas vaginitis. The presence of these organisms is sometimes associated with polyarthritis, and significant agglutination titres have been obtained from patients with Reiters syndrome and with rheumatoid arthritis.

In these experiments the L4 strain was used, cultivated on yeast extract tryptose base, enriched with 10% serum or 30% ascitic fluid. Films were made by Gram's method, re-staining with Hucker's-gentian violet.

When organisms of the twenty-eighth *in vitro* passage were used, intra-peritoneal injection of young rats gave rise to joint swellings. The maximum number showed joint swellings on the sixteenth day, and the progressive joint involvement continued at a high level until the seventh week. Organisms in pure culture could be recovered from material aspirated from the injected joints.

The administration of aurothioglucose in oil, 67 mg. per kilo, in a controlled series of rats, indicated that gold almost completely prevented the onset of the joint swellings. *David P. Nicholson.*

The Effects of 2,3-Dimercaptopropanol (BAL) on Toxicity and Excretion of Gold. KUZELL, W. C., PILLSBURY, P. L., and GELLERT, S. A. (1947). *Stanford med. Bull.*, **5**, 197.

Experiments were carried out on rats to determine the efficiency of BAL in counteracting the toxic effects of gold sodium thiosulphate and gold chloride. It was found that though BAL would protect the animals against the toxic effects of gold sodium thiosulphate, it had no such effect against the toxic action of gold chloride. Further experiments indicated that BAL promoted the urinary excretion of both compounds.
David P. Nicholson.

The Treatment of Acute Gold and Arsenic Poisoning. Use of BAL (2,3-Dimercaptopropanol, British Anti-lewisite.) COHEN, A., GOLDMAN, J., and DUBBS, A. W. (1947). *J. Amer. med. Ass.*, **133**, 749.

The Treatment of Gold Dermatitides. Use of BAL (2,3-Dimercaptopropanol). RAGAN, C., and BOOTS, R. H. (1947). *J. Amer. med. Ass.*, **133**, 752.

Ragan and Boots record experiments in which the administration to rats of BAL and gold salts was not followed by toxic effects. They then used BAL in the treatment of 5 patients suffering from dermatitis due to gold, and found in all 5 a significant excretion of gold in the urine coincident with the administration of BAL. In 4 patients in whom the dermatitis had existed for less than 4 months the pruritus ceased and the rash cleared up. In one patient with a rash for 3 months both pruritus and rash failed to respond to treatment. In 4 patients with rheumatoid arthritis symptoms were aggravated within a month of the administration of BAL.

Favourable results are also reported by Cohen, Goldman, and Dubbs, who treated 5 cases of acute poisoning due to gold and one case of acute arsenical poisoning with intramuscular injections of BAL. Transient symptoms attributable to BAL were experienced in these cases, including a sense of warmth in the mouth, salivation, flushing of the face, conjunctival injection,

lacrimation, and pains in the arms and legs, but the prompt improvement in the clinical condition was so impressive as to warrant an extensive trial of the treatment with gold intoxication. *G. R. Cameron.*

Intramuscular Copper Therapy in Chronic Inflammatory Rheumatism. (La cuprothérapie intra-musculaire dans les rhumatismes chroniques inflammatoires.) FORESTIER, J., JACQUELINE, F., and LENOIR, S. (1948). *Pr. méd.*, **56**, 351.

The authors treated 55 patients suffering from chronic inflammatory rheumatism with intramuscular injections of cupro-oxyquinoline sulphonate of methylamine; 30 were observed for about 2 years and 25 for one year. They now tend to use copper salts in cases of chronic progressive polyarthritis of less than one year's duration, cupro-allylthiourea if intravenous injection is possible, and cupro-oxyquinoline sulphonate of methylamine if the veins are poor. They think that in more chronic cases gold should at first be given.

From the figures available the efficacy of copper in arthritis of infective origin cannot be assessed. Improvement does not take place as rapidly as after gold therapy. No serious complications occurred in the 55 patients; there were slight focal reactions in 2, and 3 developed skin reactions which might have been coincidental; in some cases transient indigestion was noted.

The authors conclude that the use of copper should be further investigated, and that gold and copper may prove to be complementary forms of treatment to be used alternately in the same patient. *T. G. Reah.*

Chemotherapy in Rheumatic Polyarthritis. (Kemoterapi vid rheumatisk polyarthrit.) SVARTZ, N. (1948). *Nord. Med.*, **37**, 299.

Because salicylates are valuable symptomatically in polyarthritis and local infections sensitive to sulphonamides often cause a flare-up of the disease, the author investigated the effects of these drugs in chemical combination. A salicylic acid-azosulphapyridine compound (" salazopyrin ") was found by fluorescence microscopy to be selectively absorbed by connective tissue and to be decomposed only slowly by the body. He states that acid salicylazo compounds have a good effect on the type of acute polyarthritis seen in recent years (contrasted with classical acute rheumatism) and are also valuable in chronic polyarthritis if continued for at least several months. *A. M. M. Wilson.*

Prolonged Administration of Penicillin in Arthritis. COSS, J. A., BAUMAN, E., BOOTS, R. H., and LIPMAN, M. O. (1948). *Amer. J. Med.*, **4**, 710.

The authors studied the effects of prolonged oral administration of penicillin in 6 cases of rheumatoid arthritis of adult type, 2 of juvenile type, and 2 of rheumatoid spondylitis (Marie-Strümpell). In one case of juvenile arthritis there was striking clinical improvement with a large fall in the erythrocyte sedimentation rate. One case of rheumatoid arthritis showed moderate improvement; in the rest the treatment failed. Nausea, mild diarrhoea, localized rash, and brown furry discoloration of the tongue were observed as toxic reactions.

[No conclusions can be drawn from this small series.]

Low Grade Fever Therapy as an Adjuvant in the Treatment of Certain Types of Arthritis. DREWYER, G. E. (1948). *Arch. phys. Med.*, **29**, 284.

The 103 patients in this study, of whom 59 had rheumatoid arthritis, 29 had rheumatoid spondylitis, 7 had a combination of rheumatoid spondylitis and rheumatoid arthritis, and 8 had gonorrhoeal arthritis, received fever therapy, the general body temperature being raised to 101° F. by means of a hypertherm cabinet. The total number of sessions of low-grade fever therapy was 1,936. All the patients were given other forms of physiotherapy on the days on which they did not receive fever therapy. A group of selected cases of rheumatoid arthritis and rheumatoid arthritis and spondylitis received gold in the form of gold sodium thiomalate—5 mg. twice weekly intramuscularly on the same day as, but before, the patient received fever therapy.

In this study 90% of the patients with rheumatoid arthritis showed a remission or an improvement, this being roughly in accord with the findings of others. In the rheumatoid-spondylitis group 82% manifested a remission or an improvement, and in the group with combined rheumatoid arthritis and rheumatoid spondylitis 71·5% showed a remission or improvement, the remissions being far fewer in this group. Of the patients with gonorrhoeal arthritis 100% had remissions, all but one of these being in the chronic phase of the disease.

It is considered that the fever therapy in combination with the gold " has definite merit in that the marked increase in blood flow and capillary dilatation afford a better distribution of the injected gold salts and aid in the prevention of untoward reactions." *M. B. Ray.*

Effects of Artificially Induced Fever on the Circulation in Arthritic Patients. WAKIM, K. G., KRUSEN, F. H., and ELKINS, E. C. (1948). *Arch. phys. Med.*, **29**, 274.

Adult patients who were being treated for arthritis were studied during various types of fever treatment—cabinet fever, hot reclining baths, or typhoid vaccine administered intravenously. Tables summarize the data in 15 patients in whom a temperature of 101° F. was induced by tub baths at temperatures several degrees above that of the body for a period of about half an hour. All showed increase in blood flow. The heart rate increased, but the effects on blood pressure were variable. The data on the effect of hot humid air show that after the induction of fever a considerable increase in blood flow took place. Changes in blood pressure were variable. After intravenous typhoid vaccine the changes in circulation were: during the prodromal phase there was slight cutaneous pallor with reduction of blood flow, which became maximal at the peak of the " chill phase "; soon after the chill there was general flushing of the skin and the blood flow increased above the control level; this lasted through the period of defervescence. These prodromal symptoms and chills characterized the fever induced by intravenous typhoid vaccine but were absent when fever was induced by physical methods.

A Vascular Approach to the Treatment of Rheumatoid Arthritis : A Preliminary Report. BOUCEK, R. J., and LOWMAN, E. W. (1948). *Amer. J. med. Sci.*, **215**, 198.

The authors treated 27 patients with chronic arthritis on the assumption that disorders of vascular tone play a significant part and that procedures calculated to cause peripheral vasodilatation are likely to benefit. All cases were chronic, and 22 were of clear rheumatoid arthritis.

" Spinal pumping " (Speransky's method) was carried out in 11 patients. Three patients with rheumatoid arthritis were treated with recurrent pyrexia, induced by a combination of intravenous typhoid vaccine and autohaemotherapy twice weekly for 3 weeks. A combination

of "spinal pumping" and typhoid vaccine-autohaemotherapy was the treatment in 17 cases.

The authors now use a combination of "spinal pumping" and typhoid vaccine-autohaemotherapy; this is supplemented by nicotinic acid orally twice daily in doses sufficient to induce peripheral flushing, by physiotherapy, and by high-protein diets with intravenous plasma or protein hydrolysate in the more debilitated patients. They have had uniformly disappointing results with gold and prostigmine.

[There is little objective evidence in the paper to convince the sceptical reader that comparable long-term results might not have been obtained with physiotherapy alone.] *A. R. Kelsall.*

Prolonged Hypercalcemia and Metastatic Calcification of the Sclera following the Use of Vitamin D in the Treatment of Rheumatoid Arthritis. FROST, J. W., SUNDERMAN, F. W., and LEOPOLD, I. S. (1947). *Amer. J. med. Sci.*, **214**, 639.

The authors describe the case of a woman treated for arthritis with large doses of vitamin D for 3½ years with resulting toxic manifestations. The arthritis was of a degenerative type involving shoulders, elbows, knees, and lumbar spine. There was radiological evidence of demineralization of the pelvis. The daily dose of vitamin D had been approximately 200,000 units for the first year, 150,000 units for the second, 100,000 units for the third, and 50,000 units for the remaining 6 months. The patient started to develop pain in the left sacro-iliac region and down the left sciatic nerve after three years' treatment. She then lost 20 lb. in weight. Calcium-containing deposits were found in the conjunctiva. On the nasal and temporal sides of each cornea in the fissural zone were areas of opacity, shown by the slit-lamp to be in the superficial part of the cornea between epithelium and the anterior stroma. The lens contained spicules in the cortical area. There was radiological evidence of calcification of blood vessels posterior to the femur, but no structural abnormality of the kidneys. There was moderate anaemia. Blood urea nitrogen was 28 mg. per 100 ml., serum calcium 12·8 mg. per 100 ml., and serum alkaline phosphatase 5·5 units. Phenolsulphonphthalein excretion was only 20% in 45 minutes. "Neo-iopax" excretion was reduced in both kidneys. Calcium balance was negative whether calcium intake was high or low. Other serum electrolyte levels were within normal limits. The persistent hypercalcaemia and depressed renal function are attributed to the prolonged unsupervised administration of vitamin D. Reference is made to 2 similar cases previously reported, and warning is given against prolonged uncontrolled use of vitamin D for arthritis.
C. L. Cope.

The Ineffectiveness of Aluminium Subacetate in Rheumatoid Arthritis. BLAZER, A., FRIEDMAN, H. H., and STEINBROCKER, O. (1948). *New Engl. J. Med.*, **238**, 507.

Twelve patients with rheumatoid arthritis were treated with aluminium salts for one to two years. No appreciable improvement in subjective and objective signs of activity occurred, nor was the course of the disease significantly influenced in 11 of the 12 patients. Recalcification of the osteoporotic bones did not appear in the radiographs of 8 patients with active rheumatoid arthritis and of 3 inactive cases. In 1 case of inactive rheumatoid arthritis there were suggestive signs of slight recalcification. Repeated estimations of the blood calcium and phosphorus before and during treatment revealed no significant alterations. Aluminium subacetate demonstrated no significant therapeutic value in these patients.—(From the Authors' summary.)

Chronic Progressive Polyarthritis and Streptococcal Agglutination. (Polyarthrites chroniques évoluants et agglutination streptococcique.) COSTE, F., DELBARRE, F., and LAURENT, F. (1948). *Bull. Soc. méd. Hôp. Paris*, **64**, 513.

The authors record the results of streptococcal agglutination tests in a series of cases. They find less difference than that so far recorded in the percentage of positive reactions between the several forms of arthritis and other disorders which they studied. Thus in rheumatoid arthritis 47·4% were positive to a titre of 1 in 160 or more; in spondylitis 33%; in indeterminate polyarthritis 31·7%; and in a miscellaneous group of disorders 12·6%. They did not find any difference in thermolability between agglutinins in rheumatoid arthritis and in streptococcal infection. *Kenneth Stone.*

Autotransplantation of Joint Capsule, an Attempt to Desensitize Patients Suffering from Rheumatoid Arthritis. [In English.] NOVOTNY, H. (1948). *Acta med. scand.*, **129**, 524.

The results of treatment of arthritis by transplantation of diseased periarticular tissue are discussed.

Of the 12 patients on whom operation was performed, 11 had rheumatoid arthritis and 1 chronic gouty arthritis. The transplant was a piece of capsule obtained during synovectomy of the knee; it was placed into the subcutaneous tissue of the abdominal wall. In one instance the transplant necrosed and there was no change in the patient's condition; in the other 11 there was decrease in pain and in swelling of the joint and an increase in mobility within a few days. The patients were followed up for 9 to 17 months. In 7 instances clinical improvement had been maintained, though in 5 the erythrocyte sedimentation rate, which had gone down after operation, had returned to the pre-operation level. Improvement was pronounced in the one case of gouty arthritis.
H. A. Burt.

Xiphoid Rheumatism. (Reumatismo xifoideo.) BARCELÓ, H. (1947). *Bol. Liga argent. Reum.*, **10**, 88.

This is a rare localization of rheumatoid arthritis, characterized by spontaneous pain in the epigastric angle, increased by movements, which mobilize the xiphoid appendix, such as deep inspiration, cough, and sneezing. The cartilage is tender on palpation and very painful on pressure. This condition is easily confused with other affections producing epigastric pain, such as neuralgia of the seventh and eighth intercostal nerves, and duodenal ulcer. Two cases are described. In one the xiphoid lesion appeared in the course of rheumatoid polyarthritis in a woman with psoriasis, in the other it appeared as an exacerbation of mono-arthritis of the knee-joint in a man with a family history of gonorrhoea. *A. Lilker.*

(Osteo-arthritis)

Heberden's Nodes. VII. The Roentgenological and Clinical Appearance of Degenerative Joint Disease of the Fingers. STECHER, R. M., and HAUSER, H. (1948). *Amer. J. Roentgenol.*, **59**, 326.

Over 100 patients with Heberden's nodes were observed, 5 being described in detail. The chief points

of interest are as follows. The condition may start with formation of fluctuant myxomatous swellings which sometimes precede radiological changes; the latter may develop rapidly, though this is unusual. Periarticular soft tissues, tendinous attachments, and subchondral marrow spaces are involved as well as the joint, cartilage, and bone. Radiological changes consist of enlargement of the bone ends, loss of joint space, and bony spurs. Spurs develop from the attachment of the flexor and extensor tendons to the distal phalanges, and when large simulate in appearance a ball-and-socket joint. Spur formation is best seen in lateral views. If only postero-anterior views are taken the spurs may not be observed. The distal ends of the middle phalanges undergo marked change of bony structure which gives rise to a foamy appearance. Of patients with Heberden's nodes of the distal interphalangeal joints 40% have also degenerative disease of the proximal interphalangeal joints. It is a common mistake to regard every patient with enlargement of the latter joints as suffering from rheumatoid arthritis. Heberden's nodes tend to be associated with degenerative joint disease elsewhere. [The illustrations in this article are good.] *H. A. Burt.*

(Spondylitis)

Ankylosing Spondylitis. LENNON, W., and CHALMERS, I. S. (1948). *Lancet*, **1**, 12.

An account of 32 cases of ankylosing spondylitis is given. The frequency with which the diagnosis is missed and the importance of investigations in cases of recurrent or persistent backache in young males are emphasized. *H. F. Turney.*

Ankylosing Spondylarthritis. KUZELL, W. C. (1948). *Stanford med. Bull.*, **6**, 324.

This article is a general review of ankylosing spondylitis, its symptoms, course, pathology, and treatment. It conforms in general with accepted ideas, and nothing original is presented. *David P. Nicholson.*

Rheumatoid Spondylitis. Its Early Diagnosis and Treatment. REES, S. E., ALBERS, E. A., and NICHOLS, G. B. (1948). *Northw. Med., Seattle*, **47**, 260.

This paper deals with the diagnosis and treatment of 150 cases of ankylosing spondylitis sent to an *x*-ray therapy department. All the patients were civilians and were referred by a single general practitioner over a period of 3 years, 99 being women. *X*-ray therapy was employed in every instance. If the condition was not acute the patients were given small doses by a wide-field technique twice weekly for 6 to 8 weeks. In acute cases localized areas were treated, two larger doses (140 r to each of three regions) being given on alternate days and repeated in 6 weeks. Some 120 patients improved with deep *x*-rays, and of these 25 relapsed in 6 months. There was a decrease of 1,000 or more white cells per c.mm. after treatment in three-quarters of the cases. No mention is made of menstrual disorders following radiotherapy. *H. A. Burt.*

Paraplegia Due to Tuberculous Spondylitis. (Les paraplégies au cours de la spondylite tuberculeuse.) DE RUTTÉ, B. (1948). *Schweiz. Z. Tuberk.*, **5**, 11.

This paper reports results in the treatment of 25 patients with spinal tuberculosis and paraplegia in the Rollier institution at Leysin. Thirteen were "cured"; in 8 either signs of spasticity were lessened or the patient had not been observed long enough for the result to be considered final. Of the 4 patients who did not benefit, 2 left hospital too early, 1 died shortly after admission from secondary infection and extensive bedsores, and the fourth died of miliary tuberculosis. Treatment was on the lines laid down by Rollier—with graduated exposure to sun assisted by immobilization, if possible in the prone position, for sufficiently long periods and rehabilitation during treatment. Aspiration of abscesses and operation were avoided; plaster beds and casts are condemned. The effect of sun treatment is explained by its action on the peripheral circulation; this in turn is said to lead to beneficial action on the deep circulation, particularly in the areas of stasis and oedema which are, more often than actual bony compression, the causes of cord involvement. The prognosis on the whole is considered good and less adversely affected by bedsores, sphincter involvement, duration, or extent of paralysis than is often assumed. If, however, paralysis supervenes at a late stage of spinal destruction, or if it is flaccid or of long standing, the outlook is worse. *L. Michaelis.*

(Miscellaneous)

Heredity in Perthes's Disease. (L'hérédité de la dystrophie épiphysaire des hanches.) JEQUIER, M., and FREDENHAGEN, H. (1948). *Radiol. clin., Basel*, **17**, 92.

A pedigree covering 7 generations is given of a family in which 54 cases of Perthes's disease are known to have occurred, 14 of these being examined in detail. The disease occurred in 2 grades of severity which were considered to be due to 2 phenotypic manifestations of the same genotype. In all cases examined the disease was to some degree bilateral, and the incidence was equal in both sexes. In non-consanguineous marriages the incidence was 30% and in 2 consanguineous unions the incidence was 83% and 63%. No other morbid inheritance was discovered. In this family the inheritance of the hip dystrophy is considered to be of dominant type.

A second family is discussed whose pedigree has been previously published (*Confin. Neurol.*, 1945, **277**). In one branch of the family there was spastic paraplegia and in another degeneration of the fundus oculi, both being of inherited type. Five cases of the late effects of Perthes's disease were found amongst the members of this family and all of them had occult spina bifida. The authors postulate 3 morbid genes, but they have not yet concluded their investigations. They consider the inheritance of the hip dystrophy to be recessive. *W. J. Czyzewski.*

Perthes's Disease, Osteochondritis Dissecans, and Coxa Vara Infantium in Animal Experiment. (Perthes, Osteochondritis dissecans und Coxa vara infantum im Tierexperiment.) BURCKHARDT, E. (1948). *Helv. chir. Acta*, **15**, 3.

In 7 rabbits the author produced infractions—rather than fractures—near the femoral neck and proximal epiphysis. He studied the histological appearances of the damaged area at various stages of the healing period and found that formation of cartilaginous and fibrous callus was protracted with delayed and irregular ossification. He concludes that subliminal trauma can

produce radiological and histological changes in the proximal femoral epiphysis similar to those seen in human Perthes's diseases and coxa vara. He would assign a larger part in their parthogenesis to trauma than is generally conceded, and sees in similar processes in man one important likely cause of osteo-arthritis of the hip.

[This well-written paper rests on two assumptions which the abstracter has come to doubt: (1) that histology can be relied on in the search for pathogenesis; (2) that findings in animals—in this type of work—can be assumed to correspond to findings in human pathology.]

L. Michaelis.

Osgood-Schlatter's Disease. HUGHES, E. S. R. (1948). *Surg. Gynec. Obstet.*, **86**, 323.

The radiological appearances in 17 cases of Osgood-Schlatter's disease (3 bilateral) are recorded, with *x*-ray reproductions. The condition is considered to be due to a pathological change in the ligamentum patellae rather than in the apophysis. The condition occurs when osteoblastic activity is at its maximum, with a slightly earlier incidence in girls than boys. Trauma is regarded as the cause, and the disease is considered to be analogous to myositis ossificans at the elbow and to be a "tendinitis" rather than an "epiphysitis".

Eugénie L. Willis.

The Aetiology of Reiter's Disease. (Recherches sur l'étiologie de la Maladie de Reiter.) PASTINSZKY, É. (1947). *Acta derm.-venereol., Stockh.*, **27**, 415.

Seven cases of Reiter's disease are reported. Diarrhoea preceded the attack by 3 to 4 weeks, but at that time bacteriological examination of the stools could not be carried out. In 2 patients sero-agglutination with *Shigella dysenteriae flexner* gave titres of 1 in 200 to 1 in 400. Bacteriological examinations of conjunctival and urethral secretions were negative. Lymphogranuloma venereum was excluded by the Frei test. The syndrome is considered to be either an allergic or parallergic reaction after bacillary infection of the intestines with later participation of the other organs. Urticaria, leucopenia with a shift to the left, local eosinophilia in conjunctival and urethral secretions, or general eosinophilia, which were observed in some of the cases, were thought to confirm the allergic aetiology. The arthritis was severe, chronic, and refractory to the administration of massive doses of salicylates or cinchophen. Fever therapy (milk or sulphur injections), autohaemotherapy, calcium and ephedrine injections, glucose, and locally zinc sulphate or adrenaline, proved effective.

G. W. Csonka.

Reiter's Syndrome. Report on Nine Cases. MORRISON, R. J. G., and THOMPSON, M. (1948). *Lancet*, **1**, 636.

The authors describe 9 cases of Reiter's syndrome. No connexion with dysentery was apparent. In 4 of the patients there was no gonorrhoea, but in the other 5 gonorrhoea preceded the condition. The knee-joint was affected in all cases, the interphalangeal or metacarpo-phalangeal being the next most commonly affected joints. A rash was noted in 2 patients and hyperkeratosis of the feet in 3. Two patients (both had had gonorrhoea) developed balanitis with ulceration of the glans. It was thought that intravenous T.A.B. vaccine was of benefit in some of the patients.

(Sciatica)

Observations on the Cause and Mechanism of Symptom-production in Sciatic and Low-back Pain. FALCONER, M. A., MCGEORGE, M., and BEGG, A. C. (1948). *J. Neurol. Neurosurg. Psychiat.*, **11**, 13.

One hundred surgical cases of low back pain subjected to operation and 77 medical cases with a similar clinical picture, all examined by myelography, form the basis of the observations. It is shown that low back pain may be caused by a prolapsed disk alone and that stimulation of the prolapsed disk under local analgesia reproduces the low back pain. The prolapse could be made to fluctuate in size by weight-bearing and by hypertension of the spine. It is therefore presumed that low back pain is due to involvement of the sinu-vertebral nerve which supplies the posterior ligaments and related structures, and that the spinal rigidity and scoliosis are produced by reflex muscle spasm as a protective mechanism.

Sciatica was shown to occur only when the site of disk prolapse is such that the disk impinges upon the fifth lumbar or first sacral roots in their extrathecal course; the roots then become oedematous and longitudinally shortened. The root is pulled tight against the prolapse, longitudinal, compressive, and particularly angulation strains being thus caused. This causes a sensation of pain, while slight blocking of conductivity through the compression results in associated muscular, sensory, and reflex changes. The spontaneous remission of symptoms often observed in sciatica can result from a resolution of the neural changes without associated resolution of the disk prolapse. Myelography repeated after spontaneous recovery from symptoms (confirmed by operation in one case) usually showed that the disk prolapse had persisted apparently unchanged. Straight leg-raising was found to be restricted when the root lying over the prolapse became taut and spasms of the hamstrings resulted; this restriction could be abolished by procaine infiltration of the root at operation under local analgesia, as also could the sciatic pain and the pain induced by applying pressure stimulation to the exposed roots. Antecedent trauma was found in only 44 out of 100 cases, showing that degeneration due to premature senescent changes is the principal factor in the production of the prolapse.

A. M. Stewart-Wallace.

Pain Pathways in the Herniated Nucleus Pulposus Syndrome: A Preliminary Report. ENGLISH, R. H., and SPRIGGS, J. B. (1948). *Milit. Surg.*, **102**, 213.

On the basis of the possibility that some of the pain fibres in cases of herniated disk follow sympathetic pathways, 18 cases in which findings were compatible with the diagnosis of herniation of the nucleus pulposus were used in this study. The results suggest that in certain cases of herniation of the nucleus pulposus afferent fibres following the course of the sciatic nerve, and thence through the paravertebral sympathetic ganglia, function as pathways of pain. Possibly, too, the sympathetic fibres which are closely associated with the intervertebral disk carry impulses of pain. These fibres could be irritated by stretching of the covering of the disk and thus produce backache, but it is difficult to visualize their extension along the course of the entire sciatic nerve, which is frequently tender on palpation.

R. M. Stewart.

Transperitoneal Approach to the Intervertebral Disc in the Lumbar Area. LANE, J. D., and MOORE, E. S. (1948). *Ann. Surg.*, **127**, 537.

A technique was devised for removing diseased intervertebral disks in the lumbar region through an anterior transperitoneal approach. The objects are: (1) Removal of the entire diseased disk with the cartilaginous end-plates of the adjacent vertebrae. (2) Wedging open of the disk space with an ox-bone implant to maintain a normal interval between the vertebrae until firm bony fusion is obtained. The following advantages are listed for the authors' method: (*a*) Exposure of the entire disk space and cartilaginous end-plates. (*b*) Possibility of dealing with third, fourth, and fifth lumbar disks through the same incision. (*c*) Easier removal of the entire disk substance. (*d*) Easier control of haemorrhage, which does not occur into the spinal canal; no retraction of cord or nerve roots is necessary. (*e*) Prevention of narrowing of the disk space by the bone implant. Meticulous care must be used to exclude other diseases and intraspinal lesions, since exploration of the spinal canal and cord is not possible by this method.

The operative procedure is described. It was used in 36 cases of herniated intervertebral disk; post-operative complications occurred in 5 patients, and there were no deaths. Survey revealed that 6 patients had no symptoms; in 27 the condition was improved and in 2 unchanged; 14 patients resumed light or regular work.

The Mechanism of Origin of Lasègue's Sign. [In English.] SJÖQVIST, O. (1947). *Acta psychiat., Kbh.*, Suppl. 46, 290.

Five patients were operated on for disk protrusions under local analgesia and in a lateral position. It was shown that when the hip of the straightened leg was flexed the nerve roots and dural sac were pulled caudally and that pressure on the nerve root exerted by the protruding disk was increased when the nerve root was stretched. Lasègue's sign became negative immediately the nerve root involved was anaesthetized with procaine, showing that the sign is neural in origin and produced by purely mechanical factors.

Non-articular Rheumatism

Peritendinous Fibrosis of the Dorsum of the Hand. VAN DEMARK, R. E., KOUCKY, J. D., and FISCHER, F. J. (1948). *J. Bone Jt Surg.*, **30A**, 284.

In the two cases reported, study of sections of the swelling removed revealed the formation of fibrous tissue surrounding areas of haemorrhage or a blood cyst. The fibrous tissue was permeated with blood pigment, haemosiderin, and this had even spread into the tendon in one case. It is suggested that the recurring oedema may be accounted for by reflex dilatation of the vessels of the dorsum of the hand as described by Leriche.

Painful Shoulder. Observations on the Role of the Tendon of the Long Head of the Biceps Brachii in its Causation. HITCHCOCK, H. H., and BECHTOL, C. O. (1948). *J. Bone Jt Surg.*, **30A**, 263.

Predisposing factors, symptoms, and treatment of lesions of the long head of the biceps brachii are described.

Tricresylphosphate Polyneuritis (Review of 75 Cases). (Om trikresylfosfatpolyneurit. En redogörelse for 75 fall.) V. NANDELSTADH, O. W. (1947). *Nord. Med.*, **36**, 2379.

The author describes 75 cases of polyneuritis observed in the winter of 1944-5. The patients were mainly middle-aged men in very poor circumstances who were addicted to alcohol and other intoxicants. The greatest case incidence was during and just after a period of nation-wide prohibition of alcohol (November, 1944). There was a rapidly developing symmetrical distal paralysis affecting the limbs (the legs earlier and more than the arms) but sparing the trunk and cranial nerves. Only the ankle-jerks were regularly lost and the sensory and autonomic disturbances were mild. Recovery took months and in the severe cases was only partial. Strychnine and perhaps vitamin B_1 injections appeared to accelerate recovery in the milder cases. The cause was not certainly determined, but the clinical features were typical of Jamaica-ginger paralysis—that is, poisoning with tri*ortho*cresylphosphate, which was probably present in some of the intoxicants. This chemical was imported into Finland only during 1943; the cases began to appear in the middle of 1944 and there has been none since March, 1945. *A. M. M. Wilson.*

Sydenham's Chorea. Report of 140 Cases and Review of the Recent Literature. SCHWARTZMAN, J., MCDONALD, D. H., and PERILLO, L. (1948). *Arch. Pediat.*, **65**, 6.

A series of 140 cases of Sydenham's chorea in New York is reviewed. The ratio of girls to boys was 1·5 : 1, and of white to negro patients, 2·34 : 1. Most of the patients were between 7 and 14 years. The majority developed chorea in the first 8 months of the year. There was a great fall in the number of cases admitted in the last 5 years; the authors explain this as being due to a general improvement in living standards and prophylactic care. Two or more attacks occurred in 35·1%, negroes having fewer recurrences than white children; 23·4% had a history of rheumatic fever, and 17·1% a family history of rheumatism. Some cardiac abnormality was present in 81, but only 40 of these were shown to be organic; 50·45% had some other manifestations of rheumatism. Hemichorea was found in 7 cases, 6 being left-sided; 2 of these had a history of head injury. The best therapeutic results were obtained with pyridoxin; in two-thirds of the cases treated with this drug the condition cleared up in less than a month. The authors state, however, that the numbers are not big enough to warrant generalizations. There was no evidence that the incidence of chorea was diminished by removal of tonsils. *J. G. Jamieson.*

Penicillin Treatment of Chorea. (Korede penisilin tedavisi.) TINER, S. H. (1947). *Hastane*, **1**, 523.

Four cases of chorea were treated with from 20,000 to 30,000 units of penicillin daily till a total of 1·5 mega units had been given. Choreic movements ceased and the patients were apparently cured. *G. M. Findlay.*

General Pathological Articles

Failure of *in vitro* Inhibition of Hyaluronidase by Salicylates. SWYER, G. I. M. (1948). *Biochem. J.*, **42**, 32.

The effects of sodium salicylate, acetylsalicylic acid, and heparin on the activity of hyaluronidase in decreasing

the viscosity of solutions of potassium hyaluronate were compared. Inhibition by salicylate or acetylsalicylate occurs only in enormous concentrations (3% and 0·33% respectively), and is due to lowering of *p*H or increase in salt concentration. Heparin is completely inhibitory in a concentration of 0·0066%.

Guerra (*J. Pharmacol.*, 1946, **87**, 193) described inhibition by salicylates of spreading due to hyaluronidase in rabbits and in human beings suffering from rheumatic fever. In human beings there were violent reactions with widespread oedema; Guerra concluded that hyaluronidase played an important part in the pathogenesis of rheumatic fever and that the anti-rheumatic effect of salicylates could be explained by their inhibition of the enzyme. The present author concludes from the experiments described in this and the preceding paper that Guerra's hyaluronidase preparations contained histamine, and that salicylates inhibited the histamine effect. Since streptococci of the type believed to be responsible for rheumatic fever are producers of hyaluronidase, the author suggests that sensitivity to hyaluronidase may commonly occur in rheumatic fever. Hechter (*J. exp. Med.*, 1947, **85**, 77) has shown that the spreading activity of hyaluronidase depends on the interstitial fluid pressure; if the latter is increased, or maintained by the capillary damage produced by histamine, a substance known to play a part in hypersensitivity reactions, the results of Guerra can be explained as due to inhibition of the histamine effect. *G. Discombe.*

Other General Articles

Treatment of Rheumatic Conditions by Sex Hormones. (Traitement des affections rhumatismales par les hormones sexuelles.) COSTE, F., LACRONIQUE, B. and HOCHFELD, M. (1948). *Rev. Rhum.*, **15**, 40.

Hexoestrol or stilboestrol was given in 205 cases of osteo-arthritis; in 60% some improvement, generally transient, was evident. Hexoestrol 5 mg. or stilboestrol 3 to 4 mg. was given by mouth daily for 10 days with intervals of rest of from 1 to 3 weeks. Stilboestrol 5 mg. daily was also given intramuscularly.

Diethylstilboestrol, hexoestrol, progesterone, and testosterone were administered without effect by intramuscular injection or implantation in 47 cases of chronic, progressive polyarthritis. Twelve cases of ankylosing spondylitis were also treated; 5 patients improved but the period of observation was short. *T. G. Reah.*

Subcutaneous Implantation of Pellets of Sex Hormones in Rheumatic Conditions. (Note préliminaire sur les implantations sous-cutanées de comprimés d'hormones génitales dans les états rhumatismaux.) PIERRE-WEILL, M., and SICHÈRE, R. (1948). *Rev. Rhum.*, **15**, 33.

Rheumatic patients were treated by implantation of pellets each containing oestradiol 25 mg., or progesterone 50 or 100 mg. or testosterone 100 mg. The females were at or past the menopause, and 100 mg. of oestradiol was implanted if the uterus was absent and a maximum of 25 mg. oestradiol and 100 mg. progesterone if the uterus was present. Those suffering from paraesthesiae received oestradiol, with or without progesterone, and the results were satisfactory; the symptoms disappeared but in some cases uterine haemorrhage occurred. Patients with osteo-arthritis improved, and in half the cases there was improvement of function and disappearance of pain. The results in rheumatoid arthritis were less certain. In two cases there was improvement after oestradiol implantation and intolerance to gold disappeared; 2 others also seemed to benefit. Six cases of cervico-brachial neuralgia did not improve. There were about 60 implantations of testosterone, usually 600 to 800 mg., in men suffering from osteo-arthritis mainly between 60 and 70 years of age. In 80% the general condition improved but the joint lesions were unchanged. *T. G. Reah.*

The Toxic Manifestations of Sodium Salicylate Therapy. GRAHAM, J. D. P., and PARKER, W. A. (1948). *Quart. J. Med.*, **17**, 153.

The authors gave sodium salicylate to 40 rheumatic patients and to 30 non-rheumatic convalescents; they studied toxic manifestations in relation to plasma salicylate levels. With progressively increasing levels the following were noted: erythema, tinnitus, deafness, nausea, vomiting, albuminuria, hyperventilation, marked sweating, headache, vertigo, severe drowsiness, acetonuria, haematuria, confusion, excitement, euphoria, pulmonary oedema, severe dyspnoea, and haemorrhage. The more serious signs were noted with a salicylate level of more than 35 mg. per 100 ml.

The authors describe human and animal experiments, from which they conclude that vomiting due to salicylate is of central origin; that hyperpnoea is directly caused by salicylate; that the fall of carbon-dioxide combining power is a secondary effect; and that the vagal endings are the sites of stimulation for the hyperpnoeic effect. [The evidence for this last conclusion is unsatisfactory. We are not informed which of the manifestations arose in rheumatic patients and which in controls. It is therefore not possible to conclude which were indeed due to salicylate and which were not, especially since many of them might have arisen in untreated rheumatic fever. It is also essential to know whether or not the patient with pulmonary oedema had been given salicylate in intravenous fluid.] *G. Loewi.*

Clinical Studies in the Use of Myanesin. SCHLESINGER, E. B., DREW, A. L., and WOOD, B. (1948). *Amer. J. Med.*, **4**, 365.

The authors investigated the properties of " myanesin". They claim that a 2% solution of the drug in normal saline has numerous advantages over the 10% solution in propylene glycol and alcohol used in previous work. The only disadvantage of the former lies in its bulk, and for this reason the solution is administered by slow intravenous drip, the rate being adjusted by noting the appearance in the patient of horizontal, rotary, and then true vertical nystagmus as plasma concentration rises.

In a large series of patients 50 to 150 ml. of the 2% solution was given with a wide margin of safety. No respiratory depression was noted; there were no cardiac effects and no drastic fall in blood pressure. Phlebitis did not occur, although the same vessels were repeatedly used for injection. On the other hand, inco-ordination, lassitude, and blurring of vision often retarded resumption of normal activity for a little time after administration of the drug. The chief sites of action seem to lie in the spinal cord and brain stem, but at certain concentrations the drug has a hypnotic effect and at others it is an effective local analgesic. Its efficiency in ameliorating involuntary movement, rigidity, spasticity, and Parkinsonian tremor is of higher order than that of curare. At high concentrations, the drug has a quinidine-like

action and may produce haemolysis, but the margin of safety is comparatively wide.

In acute " low-back " pain, myanesin instantaneously relieved acute muscle spasm. In patients with acute anterior poliomyelitis reduction of muscle spasm did not relieve the pain or increase the range of limb movement, rather suggesting that pain here is due to stretching of spinal elements and that muscle spasm represents a protective splinting. Unfortunately, the evanescent nature of the effects of the drug makes it more of a laboratory tool than a therapeutic agent, but it may be of some clinical value for the treatment of reversible muscle spasm, and as an aid in manipulation of painful contractures and dislocations and in the proper evaluation of muscle deformity and contractures. *T. Semple.*

Glossopharyngeal Neuralgia. A Cause of Cardiac Arrest. RAY, B. S., and STEWART, H. J. (1948). *Amer. Heart J.*, **35**, 458.

In a case of glossopharyngeal neuralgia severe attacks of pain were associated with cardiac arrest and syncope. Section of the ninth nerve intracranially abolished both the pain and the associated cardiovascular disturbances. *R. T. Grant.*

Plantar Digital Neuritis. Morton's Metatarsalgia. NISSEN, K. I. (1948). *J. Bone Jt Surg.*, **30B**, 84.

Plantar digital neuritis was first shown by Betts to be associated with a local nodular enlargement of the digital nerve to the cleft between the third and fourth toes just proximal to its division. The author records 35 operations (8 bilateral), in 27 patients. There was pain in the sole in the region of the third and fourth metatarsal heads, or in the third or fourth toes, or at both sites; occasionally it was also referred to the second or fifth digits. Physical signs included local tenderness in all cases, occasional anaesthesia in the cleft between the third and fourth toes, and palpable swelling in 1 case. Operation was performed through a longitudinal plantar incision, and the whole nerve, with any communicating twig from the lateral plantar nerve and the vascular bundle, was removed. Complete relief was obtained in almost every case, and the scar gave no trouble. Histological examination showed that the intense fibrosis and demyelination in the nerve were secondary to a primary degenerative and thrombotic change in the digital artery. While this was presumably due to the repeated trauma of weight-bearing, it is difficult to see why one particular cleft should be affected. *A. David Le Vay.*

Pain Sensibility in Deep Somatic Structures. FEINDEL, W. H., WEDDELL, G., and SINCLAIR, D. C. (1948). *J. Neurol. Neurosurg. Psychiat.*, **11**, 113.

The authors consider that the different types of pain produced from the skin and from the stimulation of deep somatic structures can be satisfactorily explained by the difference in the arrangement of the nerve terminals in these structures, and that Lewis's postulate of two separate pain-conducting systems of nerves is not necessary. *J. W. Aldren Turner.*

Effect of Ischemia on Painful Joints. [In English.] KIRSTEIN, L., and KUGELBERG, E. (1947). *Acta psychiat., Kbh.*, Suppl. 46, 166.

It was decided to try the effect of ischaemia in reducing pain and tenderness in peripheral joints, thereby allowing greater movement. Five patients with early arthritis and periarthritis of the fingers were studied. A blood pressure cuff was inflated above the systolic level and maintained for 20 to 25 minutes; during this time the joints were rested. When the ischaemia was interrupted there was a strong reactive hyperaemia associated with paraesthesia lasting about 10 minutes. At the same time there was a marked reduction in tenderness and an increase in the range of movement. Not more than 15 treatments on alternate days should be given. *David P. Nicholson.*

Titles of other articles in the Current Literature

Vertebral Rheumatism. (Rhumatisme vertébral.) WEIL, M.-P., and SICHÈRE, R. M. (1948). *Sem. Hôp. Paris*, **24**, 1044.

Ankylosing Spondylitis and Acute Rheumatism. (Spondylarthrite ankylosante et maladie de Bouillaud.) SERRE, H., and PASSOUANT, P. (1948). *Rev. Rhum.*, **15**, 138.

Ankylosing Spondylitis and Tuberculosis. (Spondylarthrite ankylosante et tuberculose.) SERRE, H., and PASSOUANT, P. (1948). *Rev. Rhum.*, **15**, 137.

Ankylosing Spondylitis of Traumatic Origin. (Spondylarthrite ankylosante [Spondylose rhizomélique] d'origine traumatique.) GRABER-DUVERNAY, J. (1948). *J. Med. Lyon*, **29**, 321.

Destructive Menopausal Osteochondritis. (Osteochondritis destruens climacterica.) VANDENBERGHE, G. (1948). *Acta clin. belg.*, **3**, 276.

Osteoporosis of the Vertebral Column. Report of a Case. [In English.] THAYSEN, E. H. (1948). *Acta med. scand.*, Suppl. 213, 315.

Decalcifying Diffuse Myelomatosis. (Sur la myelomatose decalcifiante diffuse.) WEISSENBACH, R.-J., and LIEVRE, L.-A. (1948). *Rev. Rhum.*, **15**, 221.

Treatment of Chronic Arthropathies with Organ Lysates. (La terapia con lisati di organo nelle artropatie croniche.) CORAZZA, G., and BOTTIGLIONI, E. (1948). *Policlinico, sez. prat.*, **55**, 1077.

Employment of " Parpanit " in Rheumatic Joint Disease. (Die Verwendung von Parpanit bei rheumatischen Gelenkrankungen.) POLICZER, M. (1948). *Schweiz. med. Wschr.*, **78**, 962.

Introduction to the Pathological Physiology of Joints. (Introduction à la physiopathologie articulaire.) DALLEMAGNE, M. J., and ORY, M. (1948). *Acta physiother. rheum. belg.*, **3**, 53.

The Concept, Therapeutic Problems, and Other Clinical Features of some Rheumatic Affections of the Shoulder. (El concepto, los problemas terapéuticos y otros aspectos clínicos de algunos reumatismos de hombro.) DE VEGA, R., and CRESPO, F. (1948). *Rev. esp. Reum.*, **2**, 409.

Some Clinical and Pathological Observations in a Study of Degenerative Arthritis of the Hip Joint. HORWITZ, T. (1948). *Amer. J. Roentgen*, **60**, 225.

Symptomatology and Diagnosis of Chronic Polyarthritis in Childhood. (Sintomatologia y diagnóstico de las poliartritis crónicas en la infancia.) MARTÍNEZ GARCÍA, P. (1948). *Rev. esp. Reum.*, **2**, 353.

Physiotherapy in Rheumatoid Arthritis. (Terapéutica física en la poliartritis crónica progresiva.) PARÉS VILAHUR, J., BARCELÓ, P., and VILASECA SABATER, J. M. (1948). *Rev. esp. Reum.*, **2**, 333.

Favourable Effect of *X*-ray Therapy on Advanced Cases of Rheumatoid Arthritis. (Günstige Wirkungen der Röntgentherapie bei vorgeschrittenen Fällen von rheumatoider Arthritis.) BORAK, J., and TAYLOR, H. K. (1948). *Strahlentherapie*, **77**, 455.

Acute Bilateral Semimembranosus Bursitis in Rheumatoid Arthritis. (Bursitis aguda bilateral del semimembranoso en el curso de una artritis reumatoidea.) BARCELÓ, H. (1948). *Sem. méd.*, **55**, 659.

The Necrobiotic Nodules of the Rheumatoid Arthritis Type, with Remarks on Rheumatoid Arthritis. WEBER, F. P. (1948). *Med. Pr.*, **219**, 484.

The Optimal Physical Therapy for Rheumatoid Arthritis STENGEL, E. (1948). *N.Y. St. J. Med.*, **48**, 1028.

The Radiological Interpretation of Chronic Rheumatic Arthritis. SETH-SMITH, D. W. (1948). *Rheumatism*, **4**, 186.

On the Occurrence of Antistreptococcal O. Agglutinins in the Serum of Patients with Acute or Chronic Polyarthritis. [In English.] THULIN, K. E. (1948). *Acta path. microbiol. scand.*, **25**, 264.

Nerves of the Hip-joint. Technique of Neurotomy. (Les nerfs de l'articulation de la hanche. Technique de. leur neurotomie.) TAVERNIER, L., and PELLANDA, C. (1948). *Mém. Acad. Chir., Paris*, **74**, 264.
Dissections were performed which reveal considerable variety in the innervation of the hip.

A Case of Pseudo-tabes Due to Spondylitis. (Un cas de pseudo-tabès spondylosique de Babinski.) GARCÍN, R., and FRANÇON, F. (1948). *Rev. Rhum.*, **15**, 133.

HEBERDEN SOCIETY

The Annual General Meeting of the Heberden Society was held at the Royal Society of Tropical Medicine, London, on Saturday, Oct. 16, 1948. After election of officers and of ordinary members (as reported in the previous issue of this Journal) the Society unanimously elected to Honorary Membership Professor Sir Lionel Whitby, C.V.O., M.C., who had given the Heberden "Round" at Cambridge in 1948. Dr. Copeman then presented the Society with a framed mezzotint by Ward of the portrait of William Heberden painted by Sir William Beechy and now in the Royal College of Physicians; he was thanked by the President on behalf of the Society.

Then followed a discussion on "The Metabolism of Hyaluronic Acid in relation to Rheumatic Diseases", opened by Professor Henry Cohen and Professor C. Rimington (for the opening papers see pages 31 and 34 of this issue). Dr. J. H. Humphrey and Dr. H. J. Rogers, who had been invited to contribute to the discussion from the standpoint of their own original work in this field, then followed. (A brief account of Dr. Humphrey's and Dr. Rogers's remarks is appended.) After a discussion the meeting closed with a vote of thanks to the various speakers.

On the previous evening, with the President, Mr. S. L. Higgs, in the Chair, Dr. Philip Hench of the Mayo Clinic (an Honorary Corresponding Member of the Society) delivered the Heberden Oration on a subject for which he was awarded the Heberden Medal in 1942, "The Potential Reversibility of Rheumatoid Arthritis". (It is hoped to publish this paper in full in a later issue of this journal.)

Following a warm vote of thanks, the meeting adjourned to a reception at Claridges' Hotel where Dr. and Mrs. Hench were the Guests of Honour.

HYALURONIDASE

J. H. HUMPHREY

Having at one time worked on hyaluronic acid and hyaluronidase, and being now engaged on rheumatic fever, I have always hoped that the two lines of research would meet. However, I am far from convinced that this has yet occurred and I propose to emphasize the need for caution which Professor Cohen showed in his paper. Most preparations of hyaluronidase used in testing the effect of salicylates and the effect on sedimentation rate in rheumatic fever have been partly purified testis extracts. Such extracts contain not only enzymes which depolymerize and then further break up hyaluronic acid, but also enzymes which split chondroitin sulphuric acid, mucoitin sulphuric acid, and possibly other substances. If streptococcal hyaluronidase, which is much more specific, is used in *in vitro* attempts to lower the sedimentation rate of specimens of blood taken from patients with rheumatic fever, the

effect observed by Meyer is not obtained. This could conceivably be due to antistreptococcal hyaluronidase in the serum, but is probably not so, and Meyer himself has said later that some other factor than hyaluronidase is involved. It is notable that in nearly every site where hyaluronidase is present, mucoitin sulphuric acid (probably sulphated form of hyaluronic acid) also occurs, and often other mucopolysaccharides as well. It is impossible, therefore, at present to be certain that one is dealing with a hyaluronic acid-hyaluronidase interaction, althouhg this may be the case.

The contradictory experimental results on the *in vivo* prevention by sodium salicylate of diffusion due to hyaluronidase first described by Guerra, are possibly explained by the most interesting observation of Meyer that in animals given sodium salicylate there are produced small amounts of gentisic and gentisuric acid which are powerful inhibitors of testicular hyaluronidase *in vitro*. I have confirmed this inhibition and have also found, in agreement with Swyer, that salicylate given only half an hour before testing does not inhibit hyaluronidase in the living rabbit. It seems probable that the interval between salicylate administration and testing is an important factor here. Swyer and I have confirmed his observations that salicylate will prevent the increase in capillary permeability caused by histamine, and we have also shown that the testicular hyaluronidase most frequently used in America contains insignificant amounts of histamine, so that the effect of salicylate cannot be explained on the basis of its histamine content. Meyer has recently followed up his observations by treating rheumatic fever patients with large doses of sodium gentisate, which produced a rapid fall in fever and clinical symptoms. One cannot, however, conclude from this that the drug was acting specifically on a hyaluronidase, since it resembles sodium salicylate quite closely and might act in much the same way. Dr. James Reid has told me that large doses of ammonium chloride have an equally dramatic result in acute rheumatic fever.

Professor Cohen mentioned the increase in hyaluronidase inhibitors in acute rheumatic diseases. It has been shown that in rheumatic fever there is a well-marked rise in antibodies to streptococcal hyaluronidase, but this rise is not significantly different from that which occurs in cases of streptococcal pharyngitis and similar non-rheumatic conditions. There is another type of inhibitor in serum which may act, as does heparin, by forming an inactive combination with the enzyme. It may be relevant that in acute rheumatic fever the amount of " mucin " in the serum (estimated as total glucosamine after hydrolysis) is raised well above normal, but similar changes occur in a number of acute diseases, in particular in pneumonia.

Although it is possible to produce granulomata resembling those of rheumatic fever and even of rheumatoid arthritis by injecting trypsin into the skin of normal and rheumatic subjects, I do not know of any such changes produced by hyaluronidase preparations. It may also be relevant that pneumococci produce powerful hyaluronidase in much the same way as streptococci, but that pneumococcal infection is rarely, if ever, followed by rheumatic fever. It is important to continue work along these lines, but also important as far as is clinically possible to use as control subjects persons with acute and subacute diseases resembling rheumatic fever. The provision of suitable controls is one of the most difficult aspects of work in this field.

H. J. ROGERS

In the early studies with hyaluronidase it was usual to refer to and use preparations of the enzyme with little regard to either their source or purity. Recent work has shown that considerable care should be taken to use highly purified hyaluronidase which, if possible, have been formed by the particular organism or at least by the same genus of organisms (e.g. streptococci) as is involved in the condition under study.

The " diffusing factor ", so called, was shown by both English and American workers to possess an immunological specificity according to the source of isolation. Later, when the identity of " diffusing factor " and hyaluronidase was established, it was shown that only antibodies to the homologous enzyme were able to inhibit the hydrolysis of hyaluronic acid; examination of hyaluronidase from a limited number of streptococci showed that the enzyme had group rather than type specificity. Hence it was clear that in some ways hyaluronidase from various sources were not identical. Nevertheless, immunological differences alone were not sufficient to justify any suggestion that the hydrolysis of the substrate was not accomplished in the same way by the various enzymes. Two independent sets of studies made recently have shown, however, that enzymic hydrolysates of hyaluronic acid differ according to the source of the enzyme used. This, it is suggested, is due to the complexity of the hyaluronidase preparations. Testicular hyaluronidase probably contains at least two enzymes, one of which hydrolyses the hyaluronic acid to a disaccharide whilst the second breaks this down to monosaccharides. Similarly the total hydrolysis of hyaluronic acid by highly purified streptococcal and staphylococcal preparations of hyaluronidase is carried out by more than one enzyme. Hence we must refer to " hyaluronidases ", not " hyaluronidase ", and carefully distinguish between the various enzymes from different sources. This is more particularly important since the conditions necessary for optimal action of the enzymes show considerable variation, from source to source.

The suggestion that phosphatase may play some part in the hydrolysis of hyaluronic acid must be treated with considerable caution since active preparations of bone phosphatase do not lower the viscosity of solutions of the polysaccharide which, when carefully purified, is itself almost completely free from phosphate.

BOOK REVIEWS

Techniques in Physiotherapy. Edited by F. L. Greenhill, S.R.N. 1948. Hodder and Stoughton, Ltd., London. Pp. 222, illustrated. Price 12*s*. 6*d*.

This textbook, edited by Miss F. L. Greenhill, S.R.N., assisted by Dr. C. B. Heald, Mr. Barron, and Mr. Colson, is well written and of real practical value for it contains much recent information generally found only in books on special subjects. The first twenty-six pages are devoted to rheumatism and allied diseases, illustrated by two plates. The caption on Plate II might be altered with advantage. Two particularly interesting chapters are on physiotherapy in the treatment of chest conditions, and on the diagnosis and treatment of some nerve conditions; this last contains a short reference to electromyography. Another very useful chapter deals with some specialized methods of physiotherapy. There are also chapters on suspension therapy, based on the work of Miss Guthrie-Smith, on occupational therapy, and on exercises for abdominal conditions. All are illustrated by helpful diagrams in the text. The exact technique of each treatment is fully described, the descriptions being preceded by a short clinical account of the condition in order to explain the aims of the particular form of physiotherapy advocated.

The last chapter deals with medical practitioners and physiotherapy. In this chapter Miss Greenhill rightly points out that the majority of practitioners had no undergraduate teaching in physiotherapy and this makes it difficult for full collaboration between physiotherapists and doctors. The chapter contains a description of the direct current, induced currents, etc., commonplace to those with technical training but very useful to those who have long forgotten much of their pre-medical knowledge of physics.

This textbook fills a real want, and it will not only be of practical value to physiotherapists and doctors taking the final examination of D.P.M., but it should also be in the hands of every physician who is interested in the subject.

J. Barnes Burt.

Osteo-Arthritis of the Hip-Joint. By H. Warren Crowe. 1948. London: The Rolls House Publishing Co. Pp. 70. Price 35*s*. 6*d*.

In this monograph Dr. Warren Crowe records his views on osteo-arthritis of the hip with reference to five hundred cases. Believing that in many patients its progress can be arrested by appropriate treatment, he rightly deplores the defeatist attitude often manifested to the condition. Since he considers low-grade infection plays a part in the development of the osteo-arthritic hip, he is led to use vaccine therapy as well as the more standard measures. A stock polyvalent brew, combined at times with an autogenous addition, is employed in extremely small doses, and is claimed to be effective in a high proportion of cases. Irrespective of the questionable value of vaccines in general, the evidence adduced by the author for infection in this condition is not very convincing, and is at variance with current opinion. Other therapeutic measures recommended are intra-articular injection of acid potassium phosphate and the infiltration of painful muscles with procaine.

The book is profusely illustrated with serial *x*-ray reproductions, some of which, however, require the eye of faith to see the arrest claimed by the author. The format is attractive, and there is a felicitous quotation from Genesis on the title page.

G. R. Fearnley.

Infra-red Irradiation. By William Beaumont. 1948 : third edition. London : H. K. Lewis and Co. Pp. xii plus 162, with 32 illustrations. Price 8*s*. 6*d*.

This is a beautifullly produced and well-illustrated book and it will fit easily into the pocket. The first chapter, on terminology, and the second and third, on the physical and physiological basis of irradiation, are extremely clear and well set out, and will merit the attention of all those interested in physical treatment. They give the clearest possible exposition of the subject. The well illustrated chapter on apparatus will prove useful to many.

The second half, dealing with the clinical aspect—the treatment of common symptoms, application to disease and record of cases—is, however, not of the same standard. To describe the treatment of pain in the shoulder, pain in the knee, painful elbow, etc., as undiagnosed separate entities, seems unworthy, and the brief descriptions of diseases are even misleading. To call fibrositis simply an inflammation, with a quotation from the *British Medical Journal* of 1923, is unfortunate, and such statements as, " Infra-red irradiation invariably gives uniformly satisfactory results in so-called rheumatic fibrositis ", are sweeping in the extreme ; the implication that heat is the main treatment for rheumatoid arthritis is really dangerous. It is a great pity that such an excellent beginning should be marred by such an indifferent clinical exposition.

G. D. Kersley.

NEWS ITEMS

The Danish League against Rheumatism

We have received a summary of the work of the Danish League against Rheumatism for the years 1946 to 1948. The Danish League consists of medical and social sections and has a membership of 173,000 out of a total population of four million. The financial resources are obtained through membership fees and through a " Rheumatism Day " collection held once a year. Financial aid is given for the treatment of patients and to pay for research, and the League has influenced the Government to provide better social facilities for patients with certain rheumatic diseases, namely rheumatoid arthritis and rheumatic fever. It is expected that this will be followed by the foundation of rheumatism departments in hospitals and sanatoria. Financial aid has been given to research work on many aspects, of the rheumatic diseases

including investigations into the occurrence of Scheuermann's kyphosis, the reaction of peripheral tissues to physiotherapy, and the determination of gold concentration in blood and urine and the excretion of gold by the kidneys.

The Danish League endeavours to increase interest and knowledge of the rheumatic diseases among the lay public as well as among physicians. Medical meetings are held by the Danish Society for Rheumatology, and recent subjects for discussion have been the physiology of muscles, hyaluronidase, the veterinary joint diseases, and reactions of the peripheral circulation. A large investigation into the importance of certain occupations in the development of muscular rheumatism has been planned and will be carried out with the co-operation of the Professor of Hygiene at the University of Copenhagen.

It is clear that the Danish League against Rheumatism is an energetic body which has made considerable progress in recent years, both by educating the public in an understanding of the social importance of this group of diseases and by stimulating and financing research into some of the most important aspects of the problem.

Odontological Section of the Royal Society of Medicine

At a meeting of the Odontological section of the Royal Society of Medicine held on Nov. 22nd, 1948, a discussion on dental sepsis and rheumatic diseases was opened by Dr. G. D. Kersley. His object was to outline the principles governing the problem as seen by the physician. It was necessary to avoid the swing of the pendulum in either direction. Dr. Kersley felt that, if osteo-arthritis were excluded, the changes in rheumatism were due to "an altered reaction of the micro-organization to an invasion by a foreign protein", and that theories on aetiology were becoming more "biochemical" rather than "infective". He thought that dental infection might initiate this biochemical reaction in some 7 or 8 per cent. of cases, but that the condition might not be terminated by elimination of sepsis in all of these. After outlining and illustrating various rheumatic syndromes and suggesting the relative importance of infection in these, he pointed out the need to consider the type of rheumatism, the clinical evidence in the particular case, that is, the presence of other trigger factors and infections and the dental evidence, before giving an opinion on the need for removal of teeth. Dr. Kersley showed slides of dental radiographs illustrating types of infection, and concluded with the recommendation that dental sepsis should be looked upon as the occasional trigger in firing off some biochemical mechanism, as yet not understood, and alternatively that gross sepsis might help to sensitize the mechanism to the pull of the trigger.

Mr. J. W. Snawdon then gave a short paper on fibrositis in the muscles of mastication, a cause of pain in the region of the jaw and ear. Important diagnostic points were tenderness on palpation with one finger in the mouth and relief on infiltration with a local anaesthetic.

Mr. A. Bulleid stressed the importance of conservative measures and of treating open sepsis before removing teeth. He discussed the fallacies of *x*-rays, and also suggested the use of intradermal tests of sensitivity to organisms obtained by culture as a guide to the use of vaccines.

Mr. F. C. Hardiman had carefully charted sepsis, especially open sepsis, in the mouths of three hundred consecutive rheumatic cases at the Nuffield Unit at Manchester. He showed an instrument for measuring the depth of pockets and very interesting charts.

Mr. W. Fish stated that no live tooth could have apical infection, and again stressed the importance of paradental infection.

New York Rheumatism Association

The Fall Meeting of the New York Rheumatism Association took place at the Cornell University Medical College on Nov. 12th, 1948. Dr. Otto Steinbrocker, New York, presided.

Dr. Joseph L. Hollander, University of Pennsylvania, described the technique and clinical significance of studies on intra-articular temperature variations. Temperature recordings of various large joints, principally the knee, were done by inserting a fine thermo-couple directly into the joint through a large bore hypodermic needle. In normal subjects, the joint temperature was similar to the skin temperature. Average knee-joint temperatures in normal adult males ranged from 88 to 91° F., and the skin temperatures from 88 to 90° F. In cases of osteo-arthritis, the joint temperatures averaged 93 to 95° F., whereas the skin temperatures were 88 to 90° F. The joint temperature in rheumatoid arthritis was closely correlated to the activity of the disease. Further studies are being made on joint temperatures in other types of arthritis.

Dr. Steven M. Horvath, University of Pennsylvania, discussed the physiological considerations and effects of physical therapy on joint temperatures. Fever therapy was found to increase both the joint and skin temperatures. Hot packs applied directly to the joint resulted in an increase in skin temperature, but a decrease in intra-articular temperature of 2 to 4° F. Conversely, cold packs were found to decrease the skin temperature but to increase the intra-articular temperature. Passive motion did not change the skin temperature and had a variable effect on joint temperature. Micro-wave irradiation of the joint caused an initial rise of 7° F. in the joint, with a subsequent fall in temperature. Short wave diathermy resulted in a 6° F. rise in intra-articular temperature, with a subsequent fall in temperature. Infra-red ray irradiation caused an initial drop in joint temperature (accompanied by a rise in skin temperature) followed by a rise of joint temperature of about 3° F. Hot paraffin applied to the joint caused a slow sustained rise in joint temperature. The significance of these findings awaits further study.

The concluding paper of the evening, presented by Dr. Kaj Kalbak, Nørre Hospital, Denmark, was on the clinical application of the anti-streptolysin and haemolytic streptococcus agglutination reactions as diagnostic and prognostic aids (see Dr. Kalbak's paper in the *Annals of the Rheumatic Diseases*, 1947 **6**, 230).

Chair of Rheumatology

The Minister of Education of the French Republic has created a Chair of Rheumatology in the Faculty of Medicine of the University of Paris. This Chair is tenable at the Hopital Cochin, and the first Professor is Dr. F. Coste, Physician to the hospital and Joint Secretary of the French League against Rheumatism. It is believed that this appointment constitutes the first chair in Rheumatology to be established anywhere.